**Prior Authorization Review Panel**  
**MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.  
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**Type of Submission – Check all that apply:**

- [ ] New Policy  
- [x] Revised Policy*  
- [ ] Annual Review – NoRevisions  
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:*

**CPB 0728 Barrett's Esophagus**

This CPB has been revised to state that the following are considered experimental and investigational: (i) the use of Cytosponge for screening and surveillance of Barrett's esophagus (BE); (ii) evaluation of esophageal microbiota and mitochondrial DNA deletions for detection of BE; and (iii) volumetric laser endomicroscopy for evaluation of BE.

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<th>Name of Authorized Individual (Please type or print):</th>
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<td>Dr. Bernard Lewin, M.D.</td>
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Revised July 22, 2019
Barrett's Esophagus

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers radiofrequency ablation medically necessary for the treatment of members with Barrett's esophagus (BE) who have histological confirmation of low-grade dysplasia by two or more endoscopies three or more months apart.

Aetna considers any of the following interventions medically necessary for the treatment of members with Barrett's esophagus (BE) who have high-grade dysplasia by biopsy:

- Endoscopic mucosal resection
- Esophagectomy
- Fundoplication
- Photodynamic therapy
- Radiofrequency ablation

Aetna considers any of the following interventions experimental and investigational for the treatment of members with BE:

- Argon plasma coagulation
- Chemoradiation therapy
- Cryotherapy
- Gastrectomy
- Laser therapy
- Multi-polar electro-coagulation
- Ultrasonic therapy.

Aetna considers the following experimental and investigational because their effectiveness for these indications has not been established:

- Barrett's esophagus fluorescence in situ hybridization (FISH) assay (e.g., MolDX)
- Bariatric surgery (e.g., gastric bypass) for the treatment for BE (See CPB 0157 - Obesity Surgery (../100_199/0157.html) for medical necessity criteria for bariatric surgery)
- Biomarker panels (e.g., genetic biomarkers including mutational load, methylation biomarkers and microRNA [tissue biomarkers]) for the management of BE
- Capsule endoscopy of the esophagus for the management of BE
- Confocal laser endomicroscopy and Fuji Intelligent Chromo Endoscopy (FICE) for detecting dysplasia in BE and in post-ablation BE
- Cytosponge for screening and surveillance of BE
- Endoscopic submucosal dissection for BE and esophageal cancer
- Evaluation of esophageal microbiota and mitochondrial DNA deletions for detection of BE
- Measurements of serum levels of adipokines and insulin for the management of BE
- Optical coherence tomography for evaluation of BE
- p53 as a genomic biomarker for prediction of neoplastic progression in BE
- SOX2 expression testing for prediction of neoplastic progression in BE
- Use of markers of intestinal phenotype (CDX2, Das-1, Hep Par 1, SOX9, and villin)
- Use of methylated DNA markers for detection of BE
- Use of mucin glycoprotein immunostains
- Use of mutation analysis for risk assessment and diagnosis of BE
- Volumetric laser endomicroscopy for evaluation of BE.

See also CPB 0783 - In Vivo Analysis of Gastrointestinal Lesions (0783.html).

See also CPB 0375 - Photodynamic Therapy (../300_399/0375.html), CPB 0492 - Radiofrequency Tumor Ablation (../400_499/0492.html), and CPB 0588 - Capsule Endoscopy (../500_599/0588.html).

Background
Barrett's esophagus (BE), a complication of chronic esophagitis, is characterized by metaplasia in the epithelial lining the esophagus. The resulting cellular change is a pre-malignant phase that may lead to esophageal cancer. While the exact cause of BE is unclear, it may arise as a result of damage to the esophagus caused by chronic gastric reflux secondary to gastro-esophageal reflux disease (GERD). Thus, it is not surprising that BE is more commonly seen in patients with GERD. In addition to GERD, other risk factors for BE include age (50 years or older), ethnicity (Caucasian), and male sex. Diagnosis of BE is based on endoscopic biopsy of the esophagus. Short-segment (less than 2 to 3 cm) and long-segment (greater than 2 to 3 cm) BE are distinguished solely on the length of metaplastic epithelium above the esophago-gastric junction (Rajan et al, 2001). Emphasis is often placed on long-segment BE because these patients reportedly are at higher risk of developing adenocarcinoma than patients with short-segment BE. However, Schnell and colleagues (1992) reported that patients with short-segment BE exhibited the same incidence of esophageal cancer as their counterparts with long-segment BE. This provided a rationale for surveillance of patients with short-segment BE.

Barrett esophagus is a precancerous condition, and endoscopic biopsies to screen for high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) are recommended based on previously reported incidence rates of HGD and EAC of 0.5% and 0.9%, respectively. However, recent study findings suggest that incidence rates are lower than previously reported. To estimate the incidence of HGD or EAC in patients with BE in a population-based cohort, Hvid-Jensen, et al. (2011) analyzed data from pathology and cancer registries on 11,028 patients in Denmark who had been diagnosed with BE through endoscopic biopsy. During a median 5.2 years of follow-up, the incidence of EAC was 1.2 cases per 1000 person-years. The incidence rate of HGD or EAC combined was 2.6 cases per 1000 person-years, yielding a standardized incidence ratio of 21.1. Diagnosis of low-grade dysplasia at baseline or during follow-up increased the risk for HGD or EAC fivefold. The incidence rate of EAC among patients without low-grade dysplasia was 1.0 case per 1000 person-years (95% CI, 0.7 to 1.3) (0.1% per person-year), and the incidence rate among those with low-grade dysplasia was 5.1 cases per 1000 person-years (95% CI, 3.0 to 8.6) (0.51% per person-year). Although this study reaffirms that BE is a significant risk factor for development of EAC, the absolute risk of 0.12% is considerably lower than earlier estimates of 0.8% and, more recently, 0.5%, which have been used as a basis for current screening and surveillance recommendations. Another recent, large population-based study estimated incidence of EAC at 0.13% (Bhat, et al., 2011). On the basis of these estimates, the relative risk for EAC in patients with BE compared with the general population drops from a previously cited range of 30 to 40 to approximately 11. In an accompanying editorial, Kahrilis (2011) commented that these risk estimates have been progressively decreasing as issues of publication bias, duplicate counting, and inclusion of prevalent cancers have been taken into account.
The key to the management of BE is the level of dysplasia that endoscopic biopsies reveal. Most patients with BE will need to undergo future endoscopies to assure there is no progression of the condition. For BE patients with no signs of dysplasia on 2 consecutive endoscopic biopsies, the American College of Gastroenterology (ACG) recommended a follow-up endoscopy at 3 years. For patients with low-grade dysplasia (LGD) as the highest grade after a follow-up endoscopy with concentrated biopsies in the area of dysplasia, the ACG recommended annual endoscopy until there is no dysplasia. The finding of high-grade dysplasia (HGD), believed to be the stage that occurs before esophageal cancer, requires a repeat endoscopy or intervention, depending on the extent of the dysplasia. Focal HGD (less than 5 crypts) may be followed with 3-month surveillance (Sampliner, 2002).

The ACG guidelines also stated that the therapeutic objectives for BE are the same as those for GERD: (i) control of symptoms of GERD, and (ii) maintenance of healed mucosa. In general, patients with BE have greater esophageal acid exposure than other GERD patients, and control of symptoms may require higher than usual doses of proton pump inhibitors (PPIs). If once-daily dosing of a PPI fails to control symptoms, then twice-daily dosing should be tried. For patients who still have regurgitation despite control of esophageal acid exposure, as well as those with extra esophageal manifestations, anti-reflux surgery may be necessary. Fundoplication can effectively control reflux symptoms in most patients, but does not usually result in elimination of the pre-malignant epithelium (Sampliner, 2002).

The Society for Surgery of the Alimentary Tract (SSAT)’s guideline on the management of patients with BE (SSAT, 2002) stated that treatments include surveillance endoscopy and biopsy; medical therapy such as PPIs, H-2 receptor antagonists, and prokinetic agents; surgical anti-reflux procedure such as fundoplication (e.g., Nissen, Hill, Belsey, Dor, Toupet procedures); as well as photodynamic therapy (PDT); other energy sources; and excisional techniques. While the SSAT guideline (2002) considered PDT, other energy sources, and excisional techniques as investigational procedures, an article on BE that appeared on the ACG’s website considers PDT an accepted option for the treatment of BE (Azodo and Romero, 2006). It stated that if BE patients are diagnosed with HGD, there are 4 options:

1. Do nothing/surveillance endoscopy and biopsy. **(Note: HGD can regress to LGD or it may progress to esophageal cancer); or**
2. Increase dosage of acid suppression medications, and have another endoscopic examination in 3 months; or
3. Esophagectomy; or
4. PDT.
In June 2003, the United States Food and Drug Administration (FDA) approved PDT with Photofrin for the treatment of HGD in patients with BE who do not undergo esophagectomy. The FDA approval is based on 2-year follow-up data from phase I and II clinical studies (Overholt, 2003). The data indicated that patients who received PDT with Photofrin had an 80% chance of being cancer-free, while controls had a 50% chance of being cancer-free. These researchers found that porfimer-PDT with supplemental Nd:YAG photo-ablation and continuous treatment with omeprazole reduced the length of Barrett's mucosa, and eliminated HGD.

Furthermore, PDT plus maintenance medical therapy has been reported to lower the incidence of esophageal cancer in BE patients. In a randomized, controlled, phase III clinical trial, Overholt and colleagues (2005) examined the impact of porfimer sodium (POR) and PDT on patients with BE and with HGD. A total of 485 patients were screened, with 208 in the intent-to-treat group and 202 in the safety population. Patients were randomized on a 2:1 basis to compare PDT with POR plus omeprazole (PORPDT) with omeprazole only (OM). The main outcome measure was complete HGD ablation occurring at any time during the study period. There was a significant difference (p < 0.0001) in favor of PORPDT (77%; [106/138]) compared with OM (39%; [27/70]) in complete ablation of HGD at any time during the study period. The occurrence of esophageal adenocarcinoma in the PORPDT group (13%; n = 18) was markedly lower (p < 0.006) compared with the OM group (28%; n = 20). The safety profile showed 94% of patients in the PORPDT group and 13% of patients in the OM group had treatment-related adverse effects. The authors concluded that PORPDT in conjunction with omeprazole is an effective therapy for ablating HGD in patients with BE and in reducing the incidence of esophageal adenocarcinoma. In addition, Foroulis and Thorpe (2006) reported that PDT is effective in ablating HGD/intramucosal adenocarcinoma complicating BE in the majority of cases, while it also seems to be quite effective in treating T1b/limited T2 adenocarcinomas.

An assessment of PDT for Barrett's esophagus by the National Institute for Clinical Excellence (2004) found “Current evidence on the safety of photodynamic therapy for high-grade dysplasia in Barrett's oesophagus appears adequate to support the use of this procedure. Photodynamic therapy appears efficacious in downgrading dysplasia in Barrett's oesophagus, when used for the treatment of high-grade dysplasia (a premalignant lesion). However, its efficacy in preventing the progression of Barrett's oesophagus to invasive cancer is not clear.”

Available guidelines on the management of BE indicated that surgery may be necessary if pharmacotherapy has failed. Surgery may include fundoplication and esophagectomy. Conio and colleagues (2005) stated that esophagectomy remains the standard treatment for patients with HGD and superficial adenocarcinoma. However, since the morbidity and mortality rate for esophagectomy is high, and some patients are not surgical candidates, alternative treatments have gained popularity. In this regard, ablative techniques such as argon plasma coagulation...
(APC), cryotherapy, laser therapy, multi-polar electro-coagulation (MPEC), PDT, radiofrequency ablation, and ultrasonic therapy have been employed for this purpose. However, the effectiveness of many of these ablative interventions (except for PDT) has not been established especially the long-term control of cancer risk.

Several studies have demonstrated that endoscopic mucosal resection (EMR) is safe and effective for complete resection of superficial lesions, and offers the advantage of histopathological verification. However, larger lesions are less suitable for EMR since they often require piecemeal resection, making it impossible to be conclusive about the completeness of the resection at the lateral margins. Two devices for EMR had been cleared by the FDA through the 510(k) process for endoscopic mucosal resection in the upper gastrointestinal tract: (i) the Olympus Distal Attachment/EMR Kit, and (ii) the Cook Ireland Duette multi-band mucosectomy device.

Endoscopic treatments offer an effective alternative to esophagectomy for patients with BE and HGD. Menon, et al. (2010) conducted a comprehensive literature search to identify studies of endoscopic treatments for BE or EAC. Ninety-nine papers on 101 studies (n=3,042 participants) were included in the review. There were 12 comparative studies (seven were randomized controlled trials, five were cohort studies with uncontrolled allocation to treatment groups). The authors reported that the quality of the included studies was low, with methods and outcomes inconsistently reported across the trials. Rates of complete eradication of BE at three months post treatment were: argon plasma coagulation 85.5% (n=435, range zero to 100%), cryoablation 81.8% (n=11), thermocoagulation 100% (n=13), endoscopic mucosal resection 100% (n=1), laser ablation 77.3% (n=75, range 22.2% to 100%), multipolar electro-coagulation 88.5% (n=26) and radiofrequency ablation 69% (n=171, range 21.9% to 97.7%). Rates of complete eradication across seven techniques of photodynamic therapy varied from zero to 56.4%. Complete eradication rates of HGD at three months post-treatment were: argon plasma coagulation 85.7% (n=7), cryoablation 100% (n=1), endoscopic mucosal resection 96.3% (n=27, range 92.9% to 100%), radiofrequency ablation 90.3% (n=103, range 90.2% to 90.9%) and combined photodynamic therapy and endoscopic mucosal resection 66.7% (n=3). Rates of complete eradication across seven techniques of photodynamic therapy varied from zero to 100%. The investigators stated that further research was required to identify the endoscopic treatments that provided the best outcomes for patients with BE in relation to long-term safety, esophageal cancer prevention, continuation of drug therapy, optimal frequency of post-treatment endoscopic surveillance and quality of life after different endoscopic treatments.
Stein and Feith (2005) stated that endoscopic ablation are associated with high tumor recurrence rates and persistence of pre-malignant BE. Also, Shaheen (2005) stated that ablative therapies hold promise for individuals with superficial cancer or HGD. Most series using these modalities featured relatively short follow-up, and longer-term outcomes will be necessary to better describe the effects of these therapies.

Spechler (2005) noted that endoscopic ablative therapies may not be effective if neoplastic cells have invaded the submucosa or disseminated through mucosal lymphatic channels, and a number of studies suggested that the endoscopic therapies usually leave metaplastic or neoplastic epithelium with malignant potential behind. Limited data suggested that intensive endoscopic surveillance might be a reasonable approach for elderly or infirm patients, but some patients managed in this fashion have developed incurable esophageal cancers.

An assessment of argon plasma coagulation by the Institute for Clinical Effectiveness and Health Policy (IECS) found that, with the respect to BE, studies have not demonstrated complete disappearance of dysplastic lesions. Cases of microscopic persistence has been found, and the impact that this treatment may have in the development of malignant lesions in the long-term is unknown (Pichon Riviere et al, 2005). In a prospective, randomized, un-blinded, controlled trial (n = 40), Ackroyd et al (2004) evaluated the safety and effectiveness of APC in the ablation of BE in patients who have undergone anti-reflux surgery. Patients in the control group received endoscopic surveillance. Treatment was repeated until either no Barrett's epithelium remained or a maximum of 6 treatment sessions. One month after the final treatment, complete ablation was achieved in 12 patients. In the remaining 8 patients, a reduction of over 95% was observed. One patient died of an unrelated cause at 9 months. At one year, 1 patient with residual Barrett's epithelium regressed completely, while relapse of BE was observed in another patient because of fundoplication failure. Buried glands were observed in 35% patients at 1 month, but only 5% at 1 year. Dysplasia was never observed. In the surveillance group, partial regression was observed in 11 patients, and in 3 patients with short-segment BE, regression was complete. The length of BE increased in 2 patients. While 2 patients had LGD initially, this was not evident at 1 year. Overall, complete ablation was achieved in 63% (12/19) patients in the ablation group, and 15% (3/20) in the surveillance group (p < 0.01). These researchers concluded that APC of BE is safe and effective. The effects are durable, and buried glands may resolve with time. Moreover, the authors stated that long-term follow-up studies are needed to evaluate the impact of APC on cancer risk. A randomized trial comparing APC with PDT found that both were equally effective in eradicating Barrett's mucosa. However, APC was less effective than PDT in eradicating dysplasia within the Barrett's segment (Raganath et al, 2005).
In December 2007, the CryoSpray Ablation system (CSA Medical, Inc.) received FDA 510(k) marketing clearance as a cryosurgical tool for destruction of unwanted tissue during general surgery, specifically for endoscopic applications. The cryo-catheter applies liquid nitrogen thereby destroying unwanted tissue by the application of extreme cold to a selected site. However, the clinical effectiveness of cryotherapy in the management of patients with BE has not been established.

In a review on argon plasma coagulation, bipolar cautery, and cryotherapy for the treatment of BE, Dumot and Greenwald (2008) stated that endoscopic cryotherapy ablation is a relatively new technique with studies focusing on HGD and early-stage cancer in high-risk patients. It has an acceptable safety profile, and early results showed response in a significant number of patients in whom other modalities have failed. The authors noted that future developments with cryospray ablation technology may improve outcomes especially with uneven surfaces, with dosing capable of reaching the submucosa. Moreover, in the updated guidelines for the diagnosis, surveillance and therapy of BE by the Practice Parameters Committee of the American College of Gastroenterology, Wang and Sampliner (2008) stated that endoscopic cryotherapy has also been reported to eliminate BE, although there is very limited data about its efficacy; and cryotherapy is beginning clinical trials.

In a prospective, single-center, pilot study (n = 11), Johnston and associates (2005) assessed the safety and the effectiveness of cryotherapy on patients with a long-standing history of BE; with degrees of dysplasia ranging from none to multi-focal HGD. Subjects were also treated with 40 mg rabeprazole thrice-daily during the treatment period. Elimination of acid reflux was confirmed via 24-hour esophageal pH studies. Cryoablation was applied hemi-circumferentially to 4-cm long segments at monthly intervals, until the entire segment of BE was eliminated. There was reversal of BE in all patients. In 78 % (9/11) patients who completed the protocol, there was complete endoscopic and histologic reversal of BE. There was no subsquamous specialized intestinal metaplasia at the 6-month follow-up, and no complications occurred. The authors concluded that based on preliminary results, low-pressure spray cryoablation of BE under direct endoscopic visualization is safe and easy to perform. Its relative lack of patient discomfort and its simplicity and demonstrated effectiveness make it a modality that should be further explored in the ablation of gastrointestinal mucosal lesions such as BE and perhaps early esophageal cancer. It is interesting to note that Johnston (2005) stated that it has yet to be determined if the risks associated with ablative interventions are less than the risk of BE progressing to cancer. The author also stated that it remains to be seen if endoscopic ablative therapy can eliminate or significantly reduce the risk of cancer, eliminate the need for surveillance endoscopy, or is cost-effective.
In an open-label study, Dumot et al (2009) evaluated the safety and effectiveness of a unique non-contact method of liquid nitrogen cryoablation as measured by histological response rate and cancer-free survival. Patients with BE and HGD or intra-mucosal carcinoma (IMCA) who were deemed inoperable or who refused esophagectomy are included in this study. Age, length of BE, and previous ablation were not exclusion criteria. Cryoablation was administered every 6 weeks until endoscopic resolution. Endoscopic mucosal resection was used for pathologic staging of nodular areas before cryoablation and focal residual areas during the follow-up period. Histological response was defined by the worst pathology obtained at any level of the esophagus or gastric cardia in 1 of 3 categories: (i) incremental = absence of HGD and IMCA in all biopsy specimens, (ii) partial = residual IMCA with absence of any dysplasia, and (iii) complete = absence of any intestinal metaplasia or dysplasia. A total of 30 patients underwent ablation; 9 had undergone previous ablation or mucosectomy. Twenty-seven of 30 patients (90%) had down-grading of pathology stage after treatment. Elimination of cancer or down-grading of HGD at last follow-up was 68% for HGD and 80.0% for IMCA, with a median follow-up period of 12 months (25th percentile, 6; 75th percentile, 24). Minor adverse events included mild pain (n = 7), a low incidence of mild strictures (n = 3), and lip ulcer (n = 1). One major adverse event (perforation) in a patient with Marfan syndrome occurred with the prototype system. During follow-up, 3 of 6 patients with complete response had recurrence of dysplasia or cancer in the gastric cardia. The authors concluded that patients with BE and HGD or IMCA have a positive response to endoscopic cryotherapy at 1-year follow-up. The drawbacks of this study were that it was a small, non-randomized, single-center study with a heterogeneous cohort of patients with a relatively short follow-up (1 year). The authors stated that further study with long-term follow-up is needed and is currently under way.

Greenwald et al (2010) examined the safety, tolerability, and effectiveness of liquid nitrogen endoscopic spray cryotherapy ablation in a large cohort across multiple study sites. Parallel prospective treatment studies at 4 tertiary care academic medical centers in the U.S. assessed spray cryotherapy in patients with BE with or without dysplasia, early stage esophageal cancer, and severe squamous dysplasia who underwent cryotherapy ablation of the esophagus. All patients were contacted between 1 and 10 days after treatment to assess for side effects and complications of treatment. The main outcome measurement was the incidence of serious adverse events and side effects from treatment. Complete response for HGD (CR-HGD), all dysplasia (CR-D), intestinal metaplasia (CR-IM) and cancer (CR-C) were assessed in patients completing therapy during the study period. A total of 77 patients were treated for Barrett's HGD (58.4%), IMCA (16.9%), invasive carcinoma (13%), BE without dysplasia (9.1%), and severe squamous dysplasia (2.6%). Twenty-two patients (28.6%) reported no side effects throughout treatment. In 323 procedures, the most common complaint was chest pain (17.6%) followed by dysphagia (13.3%), odynophagia (12.1%), and sore throat (9.6%). The mean duration of any
Symptoms was 3.6 days. No side effects were reported in 48 % of the procedures (155/323). Symptoms did not correlate with age, gender, diagnosis, or to treatment early versus late in the patient's or site's experience. Logit analysis showed that symptoms were greater in those with a Barrett's segment of 6 cm or longer. Gastric perforation occurred in 1 patient with Marfan's syndrome. Esophageal stricture developed in 3, all successfully treated with dilation. In 17 HGD patients, cryotherapy produced CR-HGD, CR-D, and CR-IM of 94 %, 88 %, and 53 %, respectively. Complete regression of cancer and HGD was seen in all 7 patients with IMCA or stage I esophageal cancer. The authors concluded that endoscopic spray cryotherapy ablation using liquid nitrogen in the esophagus is safe, well-tolerated, and effective. The drawbacks of this study include (i) lack of a standardized scale to characterize post-treatment symptoms and the use of different time points to contact patients at different study sites, (ii) effectiveness data were available for only a subset of patients who completed treatment and had at least one follow-up endoscopy with biopsy during the study period, and (iii) lack of long-term follow-up data. The authors noted that studies are ongoing to further determine the safety, tolerability and effectiveness of endoscopic spray cryotherapy ablation.

In a review on endoscopic ablation of metaplasia and dysplasia in patients with BE, Wolfson (2005) stated that the FDA's approval for the use of porfimer sodium PDT was an important milestone, as this treatment has been proven to safely ablate Barrett's glandular epithelium including HGD, and significantly decrease the risk for the development of invasive cancer. The author noted that newer methods of mucosal ablation, such as the radiofrequency balloon, have been developed for the treatment of patients with BE. These newly developed techniques are able to treat large fields of glandular epithelium in a short treatment procedure. It will be extremely important to document the safety, durability, and effectiveness of these devices in preventing the development of esophageal carcinoma. Ultimately, the impact of successful Barrett's ablation on the incidence of Barrett's carcinoma, and the need for post-ablation surveillance endoscopy must be determined.

The British Society of Gastroenterology's guidelines for the diagnosis and management of BE (Watson et al, 2005) stated that endoscopic ablation remains experimental, and should be carried out only in the context of prospective, randomized trials.

Dunkin and associates (2006) ascertained the optimal treatment parameters for the ablation of human esophageal epithelium using a balloon-based bipolar radiofrequency (RF) energy electrode. Immediately prior to esophagectomy, participants underwent esophagoscopy and ablation of 2 separate, 3-cm long, circumferential segments of non-tumor-bearing esophageal epithelium using a balloon-based bipolar RF energy electrode. Subjects were randomized to one of three energy density groups: 8, 10, or 12 J/cm2. Radiofrequency energy was applied one
time (1x) proximally and two times (2x) distally. Following resection, sections from each ablation zone were evaluated using hematoxylin-eosin and diaphorase. Histological endpoints were complete epithelial ablation (yes/no), maximum ablation depth, and residual ablation thickness after tissue slough. Outcomes were compared according to energy density group and 1x versus 2x treatment. A total of 13 male subjects (aged 49 to 85 years) with esophageal adenocarcinoma underwent the ablation procedure followed by total esophagectomy. Complete epithelial removal occurred in the following zones: 10 J/cm² (2x) and 12 J/cm² (1x and 2x). The maximum depth of injury was the muscularis mucosae: 10 and 12 J/cm² (both 2x). A second treatment (2x) did not significantly increase the depth of injury. Maximum thickness of residual ablation after tissue slough was only 35 micron. The authors concluded that complete removal of the esophageal epithelium without injury to the submucosa or muscularis propria is possible using this balloon-based RF electrode at 10 J/cm² (2x) or 12 J/cm² (1x or 2x). A second application (2x) does not significantly increase ablation depth. These data have been used to select the appropriate settings for treating intestinal metaplasia in trials currently under way.

Hubbard and Velanovich (2007) presented their early experience of the effects of endoluminal ablation using radiofrequency on the reflux symptoms and completeness of ablation in post-fundoplication patients. A total of 7 patients who have had either a laparoscopic or open Nissen fundoplication and BE underwent endoscopic endoluminal ablation of the Barrett's metaplasia using the Barrx device (RF ablation). Pre-procedure, none of the patients had significant symptoms related to GERD. One to 2 weeks after the ablation, patients were questioned as to the presence of symptoms. Pre-procedure and post-procedure, they completed the GERD-HRQL symptom severity questionnaire (best possible score = 0; worst possible score = 50). Patients had follow-up endoscopy to assess completeness of ablation 3 months after the original treatment. All patients completed the ablation without complications. No patients reported recurrence of their GERD symptoms. The median pre-procedure total GERD-HRQL score was 2, compared to a median post-procedure score of 1. One patient had residual Barrett's metaplasia at 3 months follow-up, requiring re-ablation. The authors concluded that this preliminary report of a small number of patients demonstrated that endoscopic endoluminal RF ablation of Barrett's metaplasia using the Barrx device is safe and effective in patients who have already undergone anti-reflux surgery. There appears to be no disruption in the fundoplication or recurrence of GERD-related symptoms. Nevertheless, longer-term follow-up with more patients is needed.

In a study published in the *New England Journal of Medicine*, Shaheen et al (2009) evaluated if endoscopic RF ablation could eradicate dysplastic BE and reduce the rate of neoplastic progression. A total of 127 patients with dysplastic BE were randomly assigned in a 2:1 ratio to receive either RF ablation (ablation group) or a sham procedure (control group). Randomization was stratified according to the grade of dysplasia and the length of BE. Primary outcomes at 12
months included the complete eradication of dysplasia and intestinal metaplasia. In the intention-to-treat analyses, among patients with LGD, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group (p < 0.001). Among patients with HGD, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group (p < 0.001). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group (p < 0.001). Patients in the ablation group had less disease progression (3.6% versus 16.3%, p = 0.03) and fewer cancers (1.2% versus 9.3%, p = 0.045). Patients reported having more chest pain after the ablation procedure than after the sham procedure. In the ablation group, 1 patient had upper gastrointestinal hemorrhage, and 5 patients (6.0%) had esophageal stricture. The authors concluded that in patients with dysplastic BE, RF ablation was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk of disease progression.

Early studies focused exclusively on the efficacy of radiofrequency ablation for patients with low-grade dysplasia; rather, such patients commonly have been included as a subgroup in eradication trials that have involved primarily patients without dysplasia or patients with high-grade dysplasia, a feature that can confound the interpretation of study results. The report of the AIM Dysplasia Trial (Shaheen, et al., 2011) included only 32 subjects with low grade dysplasia achieving mid-term (three year) followup.

In an editorial that accompanied the afore-mentioned study, Bergman (2009) stated that "[p]ersonally, I think it is still too early to promote radiofrequency ablation for patients with nondysplastic Barrett's esophagus. Is complete response after ablation maintained over time, thus reducing the risk of progression to high-grade dysplasia or cancer? Will ablation improve patients' quality of life and decrease costs, as compared with the surveillance strategy? More important, can we define a stratification index predicting disease progression or response to therapy? We run the risk of losing the momentum to enroll patients in a trial that is required at this stage: a randomized comparison of endoscopic surveillance and radiofrequency ablation for nondysplastic Barrett's esophagus. Such a study might truly revolutionize the management of this condition and answer the question as to whether radiofrequency ablation is great just for some or justified for many".

In an editorial commenting on the study by Shaheen et al (2009), Johnson (2009) stated that these data are consistent with recent study findings demonstrating the effectiveness of photodynamic ablative therapy for patients with HGD and mucosal adenocarcinoma. The editorialist noted, however, that less-radical strategies, such as ablation and endoscopic mucosal resection only of visible lesions, seem to offer patients excellent efficacy with negligible morbidity or mortality. The editorialist stated that the finding by Shaheen et al of decreased
incidence of cancer in the radiofrequency ablation group should be viewed with caution, noting that malignancies were so rare in this cohort that a single incident cancer would have resulted in a loss of statistical significance.

Johnson (2009) stated that, although a growing amount of data seems to support the use of endoscopic ablative therapy in BE with HGD, whether the results achieved by expert academic investigators in Shaheen et al can be extrapolated to procedures performed by less-experienced endoscopists in a community-practice setting remains to be seen.

Wani et al (2009) determined the cancer incidence in BE patients after ablative therapy and compared these rates to cohort studies of BE patients not undergoing ablation. A MEDLINE search of the literature on the natural history and ablative modalities in BE patients was performed. Patients with non-dysplastic BE (ND-BE), LGD, or HGD and follow-up of at least 6 months were included. The rate of cancer in patients undergoing ablation and from the natural history data was calculated using weighted-average incidence rates (WIR). A total of 53 articles met the inclusion criteria for the natural history data. Pooled natural history data showed cancer incidence of 5.98/1,000 patient-years (95% CI: 5.05 to 6.91) in ND-BE; 16.98/1,000 patient-years (95% CI: 13.1 to 20.85) in LGD; and 65.8/1,000 patient-years (95% CI: 49.7 to 81.8) in HGD patients. A total of 65 articles met the inclusion criteria for BE patients undergoing ablation (1,457 patients, ND-BE; 239 patients, LGD; and 611 patients, HGD). The WIR for cancer was 1.63/1,000 patient-years (95% CI: 0.07 to 3.34) for ND-BE; 1.58/1,000 patient-years (95% CI: 0.66 to 3.84) for LGD; and 16.76/1,000 patient-years (95% CI: 10.6 to 22.9) for HGD patients. The authors concluded that compared to historical reports of the natural history of BE, ablation may be associated with a reduction in cancer incidence, although such a comparison is limited by likely heterogeneity between treatment and natural history studies. The greatest benefit of ablation was observed in BE patients with HGD. The authors also stated that ablation of ND-BE awaits evidence demonstrating that the costs and risks associated with the procedure are outweighed by the benefits before widespread use of this is adopted in clinical practice. Similarly, spontaneous regression of LGD has been demonstrated in the majority of BE patients, and the vast majority of subjects with ND and LGD will not benefit from ablation therapy.

In the position statement, the AGA suggests that endoscopic eradication therapy could be a therapeutic option for patients with confirmed LGD in BE, acknowledging that there are controversies about the management of dysplasia in this population and that the risk of progression to cancer can vary. The AGA supports "shared decision making" with respect to whether or not endoscopic eradication or surveillance is preferred for each individual.
Shaheen and Frantz (2010) evaluated timing and patient selection for endoscopic ablative therapy in BE. Most recent data described radiofrequency ablation (RFA), but other data pertain to PDT and other modalities. Most studies are cohort or case series. Reversion to squamous epithelium is the most common primary outcome. Cancer incidence data are scarce. Radiofrequency ablation appears well-tolerated. The main side-effect is chest pain, which can be managed with oral analgesics. Stricture occurs in 0 to 8% and is amenable to endoscopic dilatation. Infrequent side-effects include bleeding and perforation. Complete reversion to squamous epithelium occurs in more than 90% of non-dysplastic and LGD and more than 80% in HGD patients, and the treatment appears durable for at least 2 to 5 years of available follow-up. Treatment of low-grade or non-dysplastic disease may be cost-effective. Data on PDT suggest that all-cause mortality is similar to surgery for dysplastic BE. The stricture rate appears higher, and rates of complete reversion to neosquamous epithelium are lower than that of RFA, although definitive comparisons are lacking. The authors concluded that the excellent effectiveness, side-effect profile, and cost-effectiveness appear to make RFA the intervention of choice in cases of HGD. Radiofrequency ablation for LGD may be of value in young patients and/or those with long segment or multi-focal disease. Treatment of non-dysplastic BE is of uncertain value. Photodynamic therapy appears to have a higher stricture rate and to be more expensive than RFA.

Shaheen et al (2010) evaluated the influence of dysplastic BE on quality of life (QoL) and examined if endoscopic treatment of dysplastic BE with RFA improves QoL. These researchers analyzed changes in QoL in the AIM Dysplasia Trial, a multi-center study of patients with dysplastic BE who were randomly allocated to RFA therapy or a sham intervention. They developed a 10-item questionnaire to assess the influence of dysplastic BE on QoL. The questionnaire was completed by patients at baseline and 12 months. A total of 127 patients were randomized to RFA (n = 84) or sham (n = 43). At baseline, most patients reported worry about esophageal cancer (71% RFA, 85% sham) and esophagectomy (61% RFA, 68% sham). Patients also reported depression, impaired QoL, worry, stress, and dissatisfaction with the condition of their esophagus. Of those randomized, 117 patients completed the study to the 12-month end point. Compared with the sham group, patients treated with RFA had significantly less worry about esophageal cancer (p = 0.003) and esophagectomy (p = 0.009). They also had significantly reduced depression (p = 0.02), general worry about the condition of their esophagus (p ≤0.001), impact on daily QoL (p = 0.009), stress (p = 0.03), dissatisfaction with the condition of their esophagus (p ≤0.001), and impact on work and family life (p = 0.02). The authors concluded that inclusion in the treatment group of this randomized, sham-controlled trial of RFA was associated with improvement in disease-specific health-related quality of life. This improvement appears secondary to a perceived decrease in the risk of cancer. The major drawback of this study was that while the methodology employed to develop this tool provides high content validity, the test-retest reliability of the tool and its convergent validity have not been
established. Furthermore, a reference time-frame was not created in the questionnaire and it may need adjustment based on the intervention considered. Further work is needed to define the operating characteristics of this tool.

dos Santos et al (2010) reported their initial experience with RFA in association with anti-reflux procedure for Barrett’s metaplasia and LGD. A total of 14 patients (10 male and 4 female patients) presented with Barrett’s metaplasia (n = 11) or LGD (n = 3) were included in the study. Median age was 60 years (38 to 80 years). The severity of BE was classified by length (in cms), appearance (circumferential/non-circumferential), and histology (1, normal; 2, Barrett’s metaplasia; and 3, LGD). Radiofrequency ablation was performed with the HALO 360 degrees or 90 degrees systems. Median follow-up was 17 months. The mean number of ablative procedures undertaken was 2.6 (range of 1 to 6). There was no mortality, but there were 2 peri-operative complications after the anti-reflux procedure (pneumonia, n = 1; atrial fibrillation, n = 1). One patient had mild dysphagia requiring a single dilation 2 months after ablation. The mean length of BE decreased from 6.2 to 1.2 cm after treatment (p = 0.001). Barrett’s grade decreased significantly (p = 0.003). Before therapy, circumferential BE was present in 13 patients. At last endoscopy, only 1 patient had circumferential BE present. The number of RFA treatments was significantly (p < 0.05) associated with success. All patients receiving 3 or more treatments had complete resolution of Barrett’s metaplasia. The authors concluded that RFA performed either before or after an anti-reflux procedure is safe. This approach is effective for reducing or eliminating metaplasia and dysplasia. They stated that long-term studies will be necessary to determine whether this approach can provide durable control of both reflux and BE.

Fleischer et al (2010) noted that the AIM-II Trial included patients with non-dysplastic BE (NDBE) treated with RFA. Complete eradication of NDBE (complete response-intestinal metaplasia [CR-IM]) was achieved in 98.4% of patients at 2.5 years. These researchers reported the proportion of patients demonstrating CR-IM at 5-year follow-up. After endoscopic RFA of NDBE up to 6 cm, patients with CR-IM at 2.5 years were eligible for longer-term follow-up. At 5 years, these investigators obtained 4-quadrant biopsies from every 1 cm of the original extent of BE. All specimens were reviewed by 1 expert gastrointestinal pathologist, followed by focal RFA and repeat biopsy if NDBE was identified. Primary outcomes were (i) proportion of patients demonstrating CR-IM at 5-year biopsy, and (ii) proportion of patients demonstrating CR-IM at 5-year biopsy or after the single-session focal RFA. Of 60 eligible patients, 50 consented to participate. Of 1,473 esophageal specimens obtained at 5 years, 85% contained lamina propria or deeper tissue (per patient, mean of 30, standard deviation [SD] of 13). CR-IM was demonstrated in 92% (46/50) of patients, while 8% (4/50) had focal NDBE; focal RFA converted all these to CR-IM. There were no buried glands, dysplasia, strictures, or serious adverse events. Kaplan-Meier CR-IM survival analysis showed probability of maintaining CR-IM for at
least 4 years after first durable CR-IM was 0.91 (95 % confidence interval [CI]: 0.77 to 0.97) and mean duration of CR-IM was 4.22 years (standard error [SE]: 0.12). The authors concluded that in patients with NDBE treated with RFA, CR-IM was demonstrated in the majority of patients (92 %) at 5-year follow-up, biopsy depth was adequate to detect recurrence, and all failures (4/4, 100 %) were converted to CR-IM with single-session focal RFA.

There are several drawbacks with the findings of the afore-mentioned study, which included (i) a lack of concurrent control arm, (ii) a lack of histological confirmation of intestinal metaplasia prior to any focal ablation after the 1-year follow-up, (iii) a lack of standardized post 2.5-year anti-secretory medication regimen. Up to 2.5 years, all patients were provided with oral esomeprazole 40 mg per day (with escalation to twice per day for 1 month post-RFA). The inability to assess adequacy of acid suppression and compliance with medication during the post 2.5-year period, however, limits the ability to draw conclusions about the role of these factors in disease recurrence or persistent cure, (iv) there is an inherent lack of precision in identifying the precise location of the distal terminus of the esophagus and in accurately distinguishing this from the proximal extent of the stomach. This may be important regarding accurate assessment of the presence or absence of intestinal metaplasia in the esophagus after ablative therapy, and (v) the interval of 2 months from salvage RFA to subsequent biopsy to assess CR-IM after salvage was short. It is possible that after salvage RFA occult intestinal metaplasia was present that would have been detected after additional time or with further biopsy sessions.

In an editorial on RFA of BE, Falk (2010) stated "[t]he technique of RFA represents a major advance in the treatment of Barrett’s esophagus with high-grade dysplasia. With further clinical outcomes, data RFA will likely have an important role in selected individuals with well-documented low-grade dysplasia in the following settings: (i) meticulous biopsies performed on high-dose therapy with a proton pump inhibitor; (ii) confirmation by one or more expert gastrointestinal pathologists; and (iii) multifocal low grade dysplasia.....I urge the gastroenterology community to avoid the temptation of performing RFA of nondysplastic Barrett’s epithelium -- a management strategy not supported by rigorous clinical studies”.

Shaheen et al (2011) assessed long-term rates of eradication, durability of neosquamous epithelium, disease progression, and safety of RFA in patients with dysplastic BE. The investigators performed a randomized trial of 127 subjects with dysplastic BE; after cross-over subjects were included, 119 received RFA. Subjects were followed for a mean time of 3.05 years; the study was extended to 5 years for patients with eradication of intestinal metaplasia at 2 years. Outcomes included eradication of dysplasia or intestinal metaplasia after 2 and 3 years, durability of response, disease progression, and adverse events. The investigators reported that, after 2 years, 101 of 106 patients had complete eradication of all dysplasia (95 %) and 99 of
106 had eradication of intestinal metaplasia (93%). After 2 years, among subjects with initial low-grade dysplasia, all dysplasia was eradicated in 51 of 52 (98%) and intestinal metaplasia was eradicated in 51 of 52 (98%); among subjects with initial high-grade dysplasia, all dysplasia was eradicated in 50 of 54 (93%) and intestinal metaplasia was eradicated in 48 of 54 (89%). After 3 years, dysplasia was eradicated in 55 of 56 of subjects (98%) and intestinal metaplasia was eradicated in 51 of 56 (91%). Kaplan-Meier analysis showed that dysplasia remained eradicated in greater than 85% of patients and intestinal metaplasia in greater than 75%, without maintenance RFA. Serious adverse events occurred in 4 of 119 subjects (3.4%); the rate of stricture was 7.6%. Five of 119 subjects (4.2%) who received any RFA as part of this trial have experienced disease progression. In an overall observation period of 363 years, this corresponds to an annual rate of overall disease progression of 1/73 patient-years, or 1.37% per patient per year, and an annual rate of progression to EAC of 1/181 patient-years, or 0.55% per patient per year. Stratified by baseline histology at study entry, for subjects enrolled with LGD, the annual rate of overall disease progression was 1/49 patient-years, or 2.04% per patient per year, and the annual rate of progression to EAC was 1/197 patient-years, or 0.51% per patient per year. Among subjects enrolled with HGD, the annual rate of overall disease progression was 1/166 patient-years, or 0.60% per patient per year, and the annual rate of progression to EAC was 1/166 patient-years, or 0.60% per patient per year.

Phoa and colleagues (2014) found that radiofrequency ablation reduced the risk of progression to high grade dysplasia and esophageal adenocarcinoma in carefully selected patients with BE and low grade dysplasia. In this multicenter trial, 136 patients with low-grade dysplasia confirmed by expert pathologists were randomly assigned in a 1:1 ratio to undergo either radiofrequency ablation or surveillance (control group). Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma from 26.5% to 1.5%, an absolute risk reduction of 25.0%, corresponding to a number needed to treat of 4.0. Ablation also reduced the risk of progression to adenocarcinoma, from 8.8% to 1.5%, an absolute risk reduction of 7.4%. For patients in the ablation group, 92.6% of dysplasia and 88.2% of intestinal metaplasia was completely eradicated compared with 27.9% of dysplasia and 0% of intestinal metaplasia among patients in the control group. Treatment-related adverse events occurred in 19.1% of patients in the ablation group; however, these were mild. The most common adverse event was esophageal stricture (11.8%), which resolved with a median of 1 endoscopic dilation.

An accompanying editorial (Mönkemüller, 2014) noted that several important points should be emphasized before proceeding with ablation procedures for all patients with Barrett esophagus and low-grade dysplasia. Only patients with expert pathologist–confirmed low-grade dysplasia were enrolled in this trial. Of patients initially diagnosed with low-grade dysplasia, only 15% will have the diagnosis confirmed by an expert center; thus 85% of patients diagnosed with low-grade dysplasia would not be eligible for this procedure. In addition, despite expert confirmation
of low-grade dysplasia, a large percentage of patients (28%) in the study by Phoa et al had regression of their lesion over time. In this trial, histological confirmation of a 1-time low-grade dysplasia by an expert pathologist was the most important selection criteria. Thus, it is possible that selecting only patients with low-grade dysplasia on multiple endoscopies may further refine the process of selecting patients at risk of progression. The editorialist also noted that exclusive participation of expert centers in this trial may render the results less reproducible in general practice (Mönkemüller, 2014).

Bennett et al (2012) performed an international, multi-disciplinary, systematic, evidence-based review of different management strategies for patients with BE and dysplasia or early-stage EA. The authors used a Delphi process to develop consensus statements. The authors stated that, despite generally low quality of evidence, they were able to achieve consensus around several clinical statements, including: patients that receive ablative or surgical therapy require endoscopic follow-up; endoscopic therapy for HGD is preferred to surveillance; endoscopic therapy for HGD is preferred to surgery; the combination of endoscopic resection and radiofrequency ablation is the most effective therapy; and after endoscopic removal of lesions from patients with HGD, all areas of BE should be ablated. The authors stated that they focused on statements concerning HGD and EA as evidence relating to LGD is particularly weak. The authors explained that they "focused on patient populations with high-risk disease rather than including those statements about LGD, a condition for which there are even less objective data in the literature."

Das and colleagues (2009) carried out an economic analysis evaluating the cost-effectiveness of endoscopic ablation of non-dysplastic BE. A Markov model evaluated 3 competing strategies in a hypothetical 50-year-old cohort with non-dysplastic BE from a societal perspective. Strategy I -- natural history of Barrett's disease (without surveillance); strategy II -- surveillance performed according to the ACG practice guidelines; strategy III -- endoscopic ablative therapy. The model was biased against ablative therapy with a conservative estimate of complete response and continued standard surveillance even after complete ablation. All potential complications were accounted for, and an incomplete histological response after ablation was presumed to have the same risk of progression as untreated Barrett's. Transitional probabilities, discounted cost, and utility values to estimate quality-adjusted life-years (QALY) were obtained from published information. Direct costs were used in the analysis. In baseline analysis, the ablative strategy yielded the highest QALY and was more cost-effective than endoscopic surveillance. In a Monte Carlo analysis, the relative risk of developing cancer in the strategy based on endoscopic ablation was decreased compared with the other strategies. In threshold analysis, the critical determinants of cost-effectiveness of the ablative strategy were rate of complete response to ablation, total cost of ablation, and risk of progression to dysplasia. The authors concluded that
within the limits of the model, ablation for non-dysplastic BE is more cost-effective than endoscopic surveillance. They stated that clinical trials of ablative therapy in non-dysplastic BE are needed to establish its effectiveness in reducing cancer risk.

The Society of Thoracic Surgeons' practice guideline on the management of BE with HGD (Fernando et al, 2009) stated that RF ablation may be effective for ablation of HGD; however, further trials are needed before this can be recommended in preference to currently available ablative therapies.

Sharma and colleagues (2007) evaluated the dose-response, safety, and effectiveness of circumferential endoscopic ablation of BE by using an endoscopic balloon-based ablation device (HALO360 System). This study was conducted in 2 serial phases: (i) dosimetry phase and (ii) effectiveness phase. The dosimetry phase evaluated the dose-response and the safety of delivering 6 to 12 J/cm²; while the effectiveness phase used 10 J/cm² (delivered twice [x2]) for all patients, followed by EGD with biopsies at 1, 3, 6, and 12 months. A second ablation procedure was performed if BE was present at 1 or 3 months. Patients received esomeprazole 40 mg twice-daily for 1 month after ablation, and 40 mg every day thereafter. Post-ablation symptoms were quantified by using a 14-day symptom diary (scale, 0 to 100). A complete response (CR) was defined as all biopsy specimens negative for BE at 12 months. Patients were 18 to 75 years of age, with a diagnosis of BE (without dysplasia), with histopathology reconfirmation of the diagnosis within 6 months of enrollment. In the dosimetry phase, 32 patients (29 men; mean age of 56.8 years) were enrolled. Median symptom scores returned to a score of 0 of 100 by day 3. There were no dose-related serious adverse events, and the outcomes at 1 and 3 months permitted the selection of 10 J/cm² (x2) for the subsequent effectiveness phase of the study. In the effectiveness phase, 70 patients (52 men, 18 women; mean age of 55.7 years) were enrolled. Median symptom scores returned to a score of 0 of 100 by day 4. At 12 months (n = 69; mean of 1.5 sessions), a CR for BE was achieved in 70 % of patients. There were no strictures and no buried glandular mucosa in either study phase (4,306 biopsy fragments evaluated). The authors concluded that circumferential ablation of non-dysplastic BE by using this balloon-based ablation device can be performed with no subsequent strictures or buried glands and with complete elimination of BE in 70 % of patients at 1-year follow-up. They also noted that it is important to continue evaluating ablative modalities for the entire spectrum of BE disease, not just HGD. The present study represents an excellent first step, and several well-designed studies are currently underway that will address each of these potential benefits for non-dysplastic BE, LGD, and HGD.
In a review on BE and new therapeutic modalities, Sharma and Fleischer (2007) stated that as longer-term trial outcomes become available for circumferential and focal ablation, if the current safety and effectiveness result remain favorable and durable, and if cost-effectiveness studies are favorable, they may offer this therapy to selected patients with non-dysplastic intestinal metaplasia to reduce their risk for progression to dysplasia and cancer.

Roorda et al (2007) presented their early experience with RF energy ablation therapy for BE with and without dysplasia. They performed HALO(360) ablation followed by twice-daily PPI and 3-monthly surveillance for up to 12 months. If metaplasia or dysplasia were present at follow-up, the patients received a second ablation. A total of 13 patients (12 males) were treated, 3 with HGD, 4 with LGD, and 6 with non-dysplastic intestinal metaplasia. The mean baseline BE length was 6 cm (range of 2 to 12); 9 patients had an hiatal hernia and 2 had a prior fundoplication. Esophageal pH less than 4.0 for less than 4 % of time was achieved only in 5/13 patients. A mean of 1.4 ablation sessions were performed, without serious adverse events or strictures. Complete eradication of BE was achieved in 6/13 (46 %) patients. The mean endoscopic surface regression was 84 % (from a mean length of 6 +/- 1 cm to 1.2 +/- 0.5 cm, p < 0.001). Complete elimination of dysplasia was achieved in 5/7 (71 %) patients. Ablation efficacy was better in those patients who had maximal pH control (p < 0.05). HALO(360) ablation of BE with or without dysplasia is safe, well-tolerated and effective in the community setting. Follow-up ablation further reverses residual BE or dysplasia. The authors stated that early results of this technology are promising. Moreover, further study will be needed to address the durability of effect and its cost-effectiveness.

Furthermore, Ganz et al (2008) reported that endoscopic circumferential RF ablation is a promising modality for the treatment of BE that contains HGD. In this study, researchers used registry data to identify 142 patients with BE (mean length, 6 cm) and HGD who underwent circumferential ablation at any of 16 academic and community medical centers in the United States. HGD was confirmed by at least 2 pathologists. After the initial ablative therapy, patients had follow-up endoscopy at 3-month intervals with repeat circumferential ablation. Prior endoscopic mucosal resection for focal lesions had been performed in 17 % of participants. At 1-year follow-up, biopsy data were available for 92 of the 142 patients; the data showed complete HGD responses in 90.2 % and complete remission of specialized columnar metaplasia in 62.5 %. No patients were referred for esophagectomy, and no serious adverse events were reported. Commenting on this study, Johnson (2008) noted that several aspects of the study are troubling. Johnson stated that the 1-year follow-up period might not be adequate to assess the results fully, and the histologic analysis (which can vary considerably) was not standardized. The commentator noted that the lack of data on 50 of the 142 patients is concerning, and an intention-to-treat analysis would dramatically lower the "success" rates. Nonetheless, the commentator stated, the combination of endoscopic mucosal resection of focal lesions followed
by ablation of residual BE seems particularly attractive compared with esophagectomy. The commentator concluded that longer follow-up and more-complete data collection are necessary to assess more accurately the true efficacy of circumferential ablation.

Of all the academic medical centers in the United States, Mayo Clinic has performed the most RF ablation procedures to treat BE. Its website on BE (2008) states that RF ablation is a fairly new procedure that is still being studied. However, research shows that more than 70 % of those treated are free of dysplasia up to 12 months after treatment. Complications can include esophageal perforation (rupture) and strictures (narrowing). The long-term effectiveness of ablation procedures in preventing cancer is still being studied.

The American College of Gastroenterology's updated guidelines for the diagnosis, surveillance and therapy of BE (Wang and Sampliner, 2008) stated that "further evaluation of the most recent technology; radiofrequency ablation is awaited. Cryotherapy is beginning clinical trials and older technologies are becoming more refined (e.g., photodynamic therapy with the development of new agents). Documentation of the frequency and duration of the surveillance protocol after endoscopic ablation therapy requires careful study".

In a review, McAllaster et al (2009) noted that traditionally, esophagectomy has been the standard treatment for BE with HGD. This practice is supported by studies revealing unexpected adenocarcinoma in 29 to 50 % of esophageal resection specimens for HGD. In addition, esophagectomy employed prior to tumor invasion of the muscularis mucosa results in 5-year survival rates in excess of 80 %. Although esophagectomy can result in improved survival rates for early-stage cancer, it is accompanied by significant morbidity and mortality. Recently, more accurate methods of surveillance and advances in endoscopic therapies have allowed scientists and clinicians to develop treatment strategies with lower morbidity for HGD. Early data suggested that carefully selected patients with HGD can be managed safely with endoscopic therapy, with outcomes comparable to surgery, but with less morbidity. This is an especially attractive approach for patients that either can not tolerate or decline surgical esophagectomy. For patients that are surgical candidates, high-volume centers have demonstrated improved morbidity and mortality rates for esophagectomy. The addition of laparoscopic esophagectomy adds a less invasive surgical resection to the treatment armamentarium. The authors concluded that esophagectomy will remain the gold-standard treatment of BE with HGD until clinical research validates the role of endoscopic therapies.

A paper argued that ablative therapy should not be used for patients with non-dysplastic BE (Sharma et al, 2009). First, ablative therapy has not been proven to reduce the risk of developing adenocarcinoma of the esophagus. Because the lifetime cancer risk for patients with non-dysplastic BE is low 5 % to 8 % (Anderson et al, 2003), a clinical trial would require a large
number of patients and a very long follow-up to prove that ablation significantly lowers risk. The authors argued that such an undertaking might be acceptable for a treatment that is inexpensive, safe, and convenient, but current ablation techniques do not meet these criteria. They argued that ablation does not reduce or eliminate the need for ablation, because BE can recur with any form of ablation. The authors cited a report that indicated that intestinal mucosa recurred within a mean follow-up of 51 months in 66% of patients who underwent complete ablation with argon plasma coagulation (Mork et al, 2007). The authors noted that RFA has been used successfully in non-dysplastic BE; in 1 study, the procedure's complete ablation rate was 70% with minimal complications (Sharma et al, 2007). However, the authors noted that all types of ablation therapy have 3 drawbacks: (i) 3 to 5 sessions are required to eliminate Barrett mucosa completely; (ii) markers of hyper-proliferation (Ki-67 staining, p53 staining, and cyclooxygenase-2 expression) have been observed in some patients who received ablation therapy for non-dysplastic BE; because these markers are rarely found prior to ablation therapy, their presence in the neosquamous epithelium suggests that ablation poses an intrinsic risk for cancer, although long-term follow-up data are lacking; and (iii) the ablation procedures in most clinical trials to date have been performed by experts in specialized referral centers, and it is unlikely that the success rates quoted in these trials can be achieved in a community setting.

In a review of the literature, Gilbert et al (2011) stated that the general prevalence of BE is estimated at 1.6 to 3% and follows a demographic distribution similar to EAC. Both short-segment (less than 3 cm) and long-segment (greater than or equal to 3 cm) BE confer a significant risk for EAC that is increased by the development of dysplasia. The author stated that the treatment for flat high-grade dysplasia is endoscopic radiofrequency ablation therapy. The author noted that the benefits of ablation for non-dysplastic BE and BE with low-grade dysplasia have yet to be validated.

In summary, there is adequate evidence to support the use of endoscopic mucosal resection, esophagectomy, fundoplication, PDT, and RFA in the treatment of patients with BE who have dysplasia when medical therapy has failed. On the other hand, although the data to support the use of other ablative interventions in the treatment of BE are promising, more well-designed (larger, randomized, double-blinded) studies are needed to draw any definitive conclusions.

Jankowski and Odze (2009) stated that gastro-intestinal cancers account for about 25% of all cancer deaths in the Western world. There is a need for a preventive strategy that can utilize biomarkers in order to stratify patients into appropriate screening or surveillance programs. In cancer biology, the best biomarkers are germline adenomatous polyposis coli mutations, which
are highly predictive of colon cancer. In other areas, such as BE, despite early excellent success in identifying the importance of p16, p53, and aneuploidy in esophageal adenocarcinoma pathogenesis, useful biomarkers are still not widely used in clinical practice. New molecular biomarkers may be identified in the next decade, such as epigenetic methylation patterns and genetic polymorphisms. In the meantime, clinicians must rely on robust, inexpensive methods such as standard histopathology. Dysplasia is still the mainstay of cancer prediction in most inflammatory disorders of the gastrointestinal tract and is an independent marker of cancer risk.

Jin et al (2009) performed a multi-center, double-blinded validation study of 8 BE progression prediction methylation biomarkers. Progression or non-progression were determined at 2 years (tier 1) and 4 years (tier 2). Methylation was assayed in 145 non-progressors and 50 progressors using real-time quantitative methylation-specific PCR. Progressors were significantly older than non-progressors (70.6 versus 62.5 years; p < 0.001). These researchers evaluated a linear combination of the 8 markers, using coefficients from a multi-variate logistic regression analysis. Areas under the ROC curve (AUC) were high in the 2-year, 4-year, and combined data models (0.843, 0.829, and 0.840; p < 0.001, < 0.001, and < 0.001, respectively). In addition, even after rigorous over-fitting correction, the incremental AUCs contributed by panels based on the 8 markers plus age versus age alone were substantial (Delta-AUC = 0.152, 0.114, and 0.118, respectively) in all 3 models. The authors concluded that a methylation biomarker-based panel to predict neoplastic progression in BE has potential clinical value in improving both the efficiency of surveillance endoscopy and the early detection of neoplasia.

In a retrospective cohort study, Barthel et al (2010) examined the response of tumor-associated BE to chemoradiation therapy. The study cohort consisted of 43 patients with stage I to IVA esophageal adenocarcinoma associated with BE who received either neoadjuvant or definitive chemoradiation therapy and underwent either esophagectomy or surveillance. Main outcome measurement was the presence and extent of BE after chemoradiation therapy of esophageal adenocarcinoma associated with endoscopically documented pre-treatment BE. Barrett’s esophagus persisted after chemoradiation therapy in 93 % (40/43) of cases (95 % CI: 83 % to 99 %). Twenty-seven patients received neoadjuvant chemoradiation therapy before esophagectomy. Persistent BE was detected in all 27 surgical specimens (100 %). In 59 % (16/27) of the cases, there was complete pathologic tumor response. Sixteen patients received definitive chemoradiation therapy. Persistent pre-treatment BE was identified in 88 % (14/16) by surveillance endoscopy (95 % CI: 60 % to 98 %). The mean length of BE before and after chemoradiation was 6.6 cm and 5.8 cm, respectively (p = 0.38). The authors concluded that chemoradiation therapy of esophageal adenocarcinoma (EAC) does not eliminate tumor-associated BE, nor does it affect the length of the BE segment. Moreover, it should be noted that Hvid-Jensen and colleagues (2011) found that the rate of progression from BE to LGD then
to HGD is much smaller than previously thought. These investigators stated that BE is a strong risk factor for EAC, but the absolute annual risk, 0.12 %, is much lower than the assumed risk of 0.5 %, which is the basis for current surveillance guidelines.

Wani (2012) discussed the various controversies that surround the management of LGD in BE. Data on the clinical course of LGD patients with regards to rates of progression to HGD and EAC are highly variable. Recent data suggested that the rate of progression to EAC may be similar to that of patients with non-dysplastic BE (0.4 to 0.5 % per year). There is significant inter-observer variability in the diagnosis of LGD even among expert gastro-intestinal pathologists. Data on various endoscopic eradication therapies (EET) specifically in this patient population are limited. Eradication of LGD and intestinal metaplasia can be achieved by RFA. Although treatment appears to be durable for up to 3 years, progression to HGD and EAC can occur, high-lighting the need for close endoscopic surveillance even after EET. The authors concluded that there is a need to risk-stratify BE patients with LGD to identify patients most likely to progress using a reliable and objective system that incorporates clinical features, advanced imaging techniques and biomarkers. If such a high-risk group could be identified, they may benefit from EET, whereas, the majority may be managed conservatively.

Bremholm and associates (2012) noted that BE is a pre-malignant condition in the esophagus. Esophageal adenocarcinomas have the fastest increase of incidence of all solid tumors in the western world. Barrett's esophagus is defined as areas with macroscopic visible columnar epithelium and intestinal metaplasia oral of the anatomical gastroesophageal junction. The extent of the endoscopic findings is described by the Prague classification. The metaplasia is histologically confirmed by the presence of intestinal metaplasia. The diagnosis of BE can only be made by a combined macroscopic and microscopic examination. The histological description should include evaluation of dysplasia, and if present it should be classified as LGD or HGD. All patients are offered relevant anti-reflux treatment with PPI or surgery. Ablation or mucosal resection of metaplastic epithelia with or without LGD is experimental and it is not recommended outside controlled studies. Treatment of HGD and carcinoma in-situ is handled in departments treating esophageal cancer. Follow-up with endoscopy and biopsy can be offered. Follow-up endoscopy with biopsy can only be recommended after thorough information to the patients, as evidence for the value is scarce.

The National Institute for Health and Clinical Excellence (NICE)'s clinical guideline on "Ablative therapy for the treatment of Barrett's oesophagus" (NICE, 2010) recommended that "Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia, taking into account the evidence of their long-term efficacy, cost and complication rates".
The American Gastroenterological Association's medical position statement on the management of Barrett's esophagus (ACG, 2011) recommended that "endoscopic eradication therapy with radiofrequency ablation (RFA), photodynamic therapy (PDT), or endoscopic mucosal resection (EMR) rather than surveillance for treatment of patients with confirmed high-grade dysplasia within Barrett's esophagus (strong recommendation, moderate-quality evidence)."

The American Society for Gastrointestinal Endoscopy's guideline on "The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus" (ASGE, 2012) recommended that "eradication with endoscopic resection or radiofrequency ablation (RFA) be considered for flat HGD in select cases because of its superior efficacy (compared with surveillance) and side effect profile (compared with esophagectomy).

Velanovich (2012) noted that Barrett's esophagus is a pathologic change of the normal squamous epithelium of the esophagus to specialized columnar metaplasia. Barrett's esophagus is a result of prolonged exposure of the esophagus to gastro-duodenal refluxate. Although Barrett's itself is not symptomatic, and, in fact, patients with Barrett's esophagus may be completely asymptomatic, it does identify patients at higher risk of developing esophageal adenocarcinoma. Traditionally, anti-reflux surgery was reserved for patients with symptoms, because it was believed that anti-reflux surgery did not eliminate Barrett's esophagus and reduce cancer risk. Rationale for the treatment of Barrett's esophagus beyond treating symptoms of gastro-esophageal reflux disease stems from the hope to decrease, if not eliminate, the risk of adenocarcinoma. Treatment options ranged from medical acid suppression without surveillance to resection. Ablation, particularly endoscopic radiofrequency ablation, has become the standard of care for Barrett's esophagus with high-grade dysplasia. Its role in non-dysplastic or low-grade dysplastic Barrett's is less clear. Combined endoscopic mucosal resection with ablation is effective in nodular high-grade Barrett's esophagus. Resection should be reserved for patients with persistent high-grade dysplasia despite multiple attempts at endoscopic ablation or resection or for patients with evidence of carcinoma.

Spechler (2013) stated that the American Gastroenterological Association (AGA) defines Barrett's esophagus as the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the squamous epithelium that normally lines the distal esophagus. Although cardiac mucosa may be metaplastic, its malignant predisposition is not clear, and the AGA still requires the demonstration of intestinal metaplasia (with goblet cells) for a diagnosis of Barrett's esophagus. The AGA generally recommends endoscopic eradication therapy for patients with high-grade dysplasia, who otherwise develop esophageal adenocarcinoma at the rate of 6 % per year. Endoscopic therapy is often curative for mucosal neoplasms in Barrett's esophagus because the risk of lymph node metastases is only 1 to 2 %. American gastroenterologists generally do not recommend endoscopic therapy for patients...
whose neoplasms involve any portion of the submucosa because of the high rate of lymph node metastases that has been described in these cases. The management of low-grade dysplasia is disputed because of poor agreement among pathologists on the diagnosis and because of contradictory data on the natural history, but the AGA recommends that radiofrequency ablation (RFA) should be a therapeutic option for patients with confirmed low-grade dysplasia in Barrett's esophagus. Arguments for using RFA to treat non-dysplastic Barrett's metaplasia are based on the premise that RFA decreases cancer risk, but no study has established that premise. In the absence of definitive data, concerns about the frequency and importance of buried metaplastic glands and recurrent metaplasia should temper enthusiasm for treating non-dysplastic Barrett's esophagus with RFA.

Almond and Barr (2014) stated that the management of BE and associated neoplasia has evolved considerably in recent years. Modern endoscopic strategies including endoscopic resection and mucosal ablation can eradicate dysplastic Barrett’s and prevent progression to invasive esophageal cancer. However, several aspects of Barrett's management remain controversial including the stage in the disease process at which to intervene, and the choice of endoscopic or surgical therapy. These investigators performed a review of articles pertaining to the management of BE with or without associated neoplasia in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Medline, Embase and Cochrane databases were searched to identify literature relevant to 8 pre-defined areas of clinical controversy. The following search terms were used: Barrett's esophagus; dysplasia; intramucosal carcinoma; endotherapy; endoscopic resection; ablation; esophagectomy. A significant body of evidence exists to support early endoscopic therapy for HGD. Although not supported by randomized controlled trial (RCT) evidence, endoscopic therapy is now favored ahead of esophagectomy for most patients with HGD. Focal intramucosal (T1a) carcinomas can be managed effectively using endoscopic and surgical therapy, however surgery should be considered the 1st line therapy where there is sub-mucosal invasion (T1b). The authors stated that treatment of LGD is not supported at present due to widespread over-reporting of the disease. The role of surveillance endoscopy in non-dysplastic Barrett's remains controversial.

Almond et al (2014) identified systematically all reports of endoscopic treatment of LGD, and assessed outcomes in terms of disease progression, eradication of dysplasia and intestinal metaplasia, and complication rates. These researchers performed a systematic review of articles reporting endoscopic treatment of LGD in accordance with PRISMA guidelines. Medline and Embase databases were searched to identify the relevant literature. Rates of complete eradication of intestinal metaplasia (CE-IM) and dysplasia (CE-D) were reported. The pooled incidence of progression to cancer was calculated following endoscopic therapy. A total of 37 studies met the inclusion criteria, reporting outcomes of endoscopic therapy for 521 patients with
The pooled incidence of progression to cancer was 3.90 (95% CI: 1.27 to 9.10) per 1,000 patient-years. CE-IM and CE-D were achieved in 67.8 (95% CI: 50.2 to 81.5) and 88.9 (83.9 to 92.5) % of patients, respectively. The commonest adverse event was stricture formation. The authors concluded that reports of endoscopic therapy were heterogeneous and follow-up periods were short. There is a high likelihood of historical over-diagnosis of LGD. Endoscopic therapy, particularly RFA, appears safe and effective at eradicating LGD, but does not eliminate the risk of progression to cancer.

In a review on “Barrett’s esophagus” published in the New England Journal of Medicine, Spechler and Souza (2104) stated that some physicians have proposed that RFA should be offered to all patients with BE, dysplastic or non-dysplastic, arguing that endoscopic surveillance is not an effective cancer-prevention strategy and that RFA is safe and effective for eradicating Barrett’s metaplasia. However, the effectiveness of RFA for preventing cancer in patients with ND-BE has not been established in long-term studies, and there are at least 2 reasons why the risk of cancer may not be eliminated, even when RFA eradicates all visible evidence of Barrett's metaplasia. First, patients with BE frequently have metaplastic glands in the lamina propria underneath the esophageal squamous epithelium, usually within 1 cm of its junction with metaplasia. The overlying squamous epithelium hides this sub-squamous intestinal metaplasia from the endoscopist and may protect it from RFA. The rate at which sub-squamous intestinal metaplasia progresses to a malignant state is not known, but cancers have been found in these sub-squamous metaplastic glands. Another reason to suspect that RFA might not eliminate the risk of cancer is the observation that Barrett's metaplasia can recur over time. Early studies suggested that the recurrence rate after RFA was low, but more recent studies have shown recurrences of Barrett's metaplasia, sometimes with dysplasia and cancer, in up to 33 % of patients at 2 years. The long-term cancer risk associated with recurrent Barrett's metaplasia after RFA is not known. These investigators noted that since the frequency and importance of sub-squamous intestinal metaplasia and recurrent Barrett's metaplasia have not yet been determined, the effectiveness of RFA for cancer prevention in patients with ND-BE is unclear. They stated that these uncertainties suggest that patients should continue to undergo endoscopic surveillance even after apparently successful eradication of metaplasia by means of RFA. Moreover, they noted that one study used a decision-analytic Markov model to explore the cost-effectiveness of RFA for 50-year old men with BE and concluded that it was cost-effective for those with dysplasia but not for those with non-dysplastic metaplasia. At this time, the authors do not recommend RFA for the general population of patients with ND-BE.

Fuji Intelligent Chromo Endoscopy (FICE)
According to the manufacturer, "[a]s a basic principle, F.I.C.E. imaging is implemented based on Spectral Estimation Technology. Spectral Estimation Technology takes an ordinary endoscopic image from the video processor and arithmetically processes, estimates and produces an image of a given, dedicated wavelength of light. Now, for the first time ever, this technology is put to practical use in the field of endoscopy by Fujinon. The expected advantage of this new digital processing system is a dramatic enhancement in the detection and identification of pathologic changes. The F.I.C.E. system is expected to enable doctors to supplement differences in experiences and to diagnose clinical findings more accurately than ever before. In contrast to a system in which an optical filter is used, this digital processing system is able to switch over between an ordinary image and a F.I.C.E. image in a splitsecond."

In a review on advanced imaging of the gastro-intestinal tract Goetz and Kiesslich (2009) stated that digital chromoendoscopy techniques such as narrow band imaging, i-scan, or FICE offer new possibilities of easily and reversibly obtaining enhanced tissue contrast. Advanced imaging techniques have provided the endoscopist with an armamentarium of novel modalities for detection, characterization and microscopy of lesions during endoscopy. In addition, functional and molecular imaging give insight into dynamic processes of tissues in their natural surroundings.

A metaanalysis by Qumseya, et al. (2014) found that advanced imaging technologies increased diagnostic yield by 34 percent. The increase in yield was similar for FICE, chromoendoscopy and narrow-band imaging. However, there are insufficient data to determine whether this increase in diagnostic yield results in improved clinical outcomes.

According to ClinicalTrials.gov, a service of the National Institutes of Health, a clinical trial on the role of the FICE for the detection of dysplasia in BE and in post-ablation BE was suspended recently (2011).

**Germline Mutations in Barrett Esophagus/Esophageal Adenocarcinoma**

Barrett esophagus occurs in 1% to 10% of the general population and is believed to be the precursor of EAC. The incidence of EAC has increased 350% in the past 30 years without clear etiology. Finding pre-disposition genes may improve pre-morbid risk assessment, genetic counseling, and management. Genome-wide multi-platform approaches may lead to the identification of genes important in BE/EAC development. Orloff et al (2011) identified risk alleles or mutated genes associated with BE/EAC. Model-free linkage analyses of 21 concordant-affected sibling pairs with BE/EAC and 11 discordant sibling pairs (2005 to 2006) were carried out. Significant germline genomic regions in independent prospectively accrued series of 176 white patients with BE/EAC and 200 ancestry-matched controls (2007 to 2010) were validated.
and fine mapped. Integrating data from these significant genomic regions with somatic gene expression data from 19 BE/EAC tissues yielded 12 “priority” candidate genes for mutation analysis (2010). Genes that showed mutations in cases but not in controls were further screened in an independent prospectively accrued validation series of 58 cases (2010). Main outcome measures were identification of germline mutations in genes associated with BE/EAC cases, and functional interrogation of the most commonly mutated gene. Three major genes, MSR1, ASCC1, and CTHRC1 were associated with BE/EAC (all p < 0.001). In addition, 13 patients (11.2 %) with BE/EAC carried germline mutations in MSR1, ASCC1, or CTHRC1. MSR1 was the most frequently mutated, with 8 of 116 (proportion, 0.069; 95 % CI: 0.030 to 0.130; p < 0.001) cases with c.877C>T (p.R293X). An independent validation series confirmed germline MSR1 mutations in 2 of 58 cases (proportion, 0.035; 95 % CI: 0.004 to 0.120; p = 0.09). MSR1 mutation resulted in CCND1 up-regulation in peripheral-protein lysate.

Immunohistochemistry of BE tissues in MSR1-mutation carriers showed increased nuclear expression of CCND1. The authors concluded that MSR1 was significantly associated with the presence of BE/EAC in derivation and validation samples, although it was only present in a small percentage of the cases. They stated that future independent studies are needed to replicate their data in other patient populations to confirm the conclusions. Furthermore, larger cohort studies may be necessary to determine the usefulness of these genes and their variant in risk assessment and pre-morbid diagnosis.

MicroRNAs as Biomarkers for Barrett’s Esophagus Progression

Bansal et al (2011) evaluated feasibility and clinical accuracy of novel microRNA (miRNA) biomarkers for prediction of BE dysplasia. Paired fresh-frozen and hematoxylin/eosin specimens from a prospective tissue repository where only biopsies with the lesion of interest (i.e., intestinal metaplasia (IM) or HGD/EAC) occupying greater than 50 % of biopsy area were included.

Tissue miRNA expression was determined by microarrays and validated by quantitative reverse transcription-PCR (qRT-PCR). Three groups were compared: group A, IM tissues from BE patients without dysplasia; group B, IM tissues from group C patients; and group C, dysplastic tissues from BE patients with HGD/EAC. Overall, 22 BE patients, 11 with and without dysplasia (mean age 64 +/- 8.2 and 63 +/- 11.6 years, respectively, all Caucasian males) were evaluated. Nine miRNAs were identified by high-throughput analysis (miR-15b, -21, -192, -205, 486-5p, -584, -1246, let-7a, and -7d) and qRT-PCR confirmed expression of miR-15b, -21, 486-5p, and let-7a. Two of 4 miRNAs (miR-145 and -203, but not -196a and -375) previously described in BE patients also exhibited differential expression. Sensitivity and specificity of miRNAs for HGD/EAC were miR-15b: 87 and 80 %, miR-21: 93 and 70 %, miR-203: 87 and 90 %, miR-486-5p: 82 and 55 %, and miR-let-7a: 88 and 70 %, respectively. MiRNA-15b, -21, and -203 exhibited field effects (i.e., groups A and B tissues while histologically similar yet exhibited
different miRNA expression). The authors concluded that this pilot study demonstrated feasibility of miRNAs to discriminate BE patients with and without dysplasia with reasonable clinical accuracy. However, the specific miRNAs need to be evaluated further in future prospective trials.

Revilla-Nuin et al (2013) identified a set of miRNAs as prognostic molecular biomarkers for the progression of BE to EAC to rationalize the surveillance programs in patients with BE. Micro-RNAs associated with progression of BE to EAC were identified using miRNA sequencing analysis. Further validation by qRT-PCR was performed in 2 groups of BE patients who either developed or did not develop adenocarcinoma after at least 5 years of follow-up. A total of 23 miRNAs were identified by miRNA sequencing analysis in the carcinogenesis process associated with BE. qRT-PCR analysis using independent tissue samples confirmed differential expression for 19 of them (miR-let-7c, 7, 146a, 149, 153, 192, 192, 194, 194, 196a, 196b, 944). However, only miR-192, 194, 196a, and 196b showed a significantly higher expression in BE samples from patients with progression to EAC compared with those who did not progress to EAC. The authors concluded that these findings suggested that these miRNAs could be useful biomarkers to predict the progression of the disease and should be further evaluated in clinical trials of BE progression in a large-scale study.

Mallick et al (2016) reviewed studies that have investigated this to identify microRNAs with high biomarker potential for screening and disease monitoring in BE. PubMed and Embase databases were searched for studies that quantified esophageal epithelial microRNAs. Publications reporting microRNA comparisons of normal, non-dysplastic BE, BE with HGD, and EAC tissues using both unbiased discovery and independent validation phases were reviewed. A total of 11 studies on microRNA expression differences between normal epithelium and non-dysplastic BE (7 studies), HGD (4) or EAC (7), or between non-dysplastic BE and HGD (3) or EAC (6) were identified, and the findings of their validation phase were analyzed. Increased miR-192, -194, and -215, and reduced miR-203 and -205 expression in BE compared to normal was noticed by all 4-6 of the 7 studies that examined these microRNAs. In heterogeneity tests of the reported fold-change values, the I (2) statistics were 7.9 to 17.1 % (all p < 0.05). Elevated miR-192, -194, and -215, and diminished miR-203 and -205 levels were also noted for comparisons of HGD or EAC against normal. In contrast, a consistent microRNA expression difference was absent for the comparisons of HGD or EAC against BE. The authors concluded that microRNAs miR-192, -194, -203, -205, and -215 are promising tissue biomarkers for diagnosing BE. Cross-sectional data suggested that microRNAs may have a limited role in separating BE from HGD/EAC epithelia but need further testing in longitudinal follow-up studies.

Confocal Laser Endomicroscopy
Probe-based confocal laser endomicroscopy (pCLE) is an imaging technique that allows real-time in-vivo histological assessment of BE.

In a prospective, multi-center, randomized, clinical trial, Wallace and colleagues (2012) evaluated if use of pCLE in addition to high-definition white light (HDWL) could aid in determination of residual BE. After an initial attempt at ablation, patients were followed-up either with HDWL endoscopy or HDWL plus pCLE, with treatment of residual metaplasia or neoplasia based on endoscopic findings and pCLE used to avoid over-treatment. Main outcome measurements included the proportion of optimally treated patients, defined as those with residual BE who were treated and had complete ablation plus those without BE who were not treated and had no evidence of disease at follow-up. The study was halted at the planned interim analysis based on a priori criteria. After enrollment was halted, all patients who had been randomized were followed to study completion. Among the 119 patients with follow-up, there was no difference in the proportion of patients achieving optimal outcomes in the 2 groups (15/57, 26 % for HDWL; 17/62, 27 % with HDWL + pCLE). Other outcomes were similar in the 2 groups. The authors concluded that this study yielded no evidence that the addition of pCLE to HDWL imaging for detection of residual BE or neoplasia can provide improved treatment.

Bertani et al (2012) stated that many endoscopic imaging modalities have been developed and introduced into clinical practice to enhance the diagnostic capabilities of upper endoscopy. In the past, detection of dysplasia and carcinoma of esophagus had been dependent on biopsies taken during standard white-light endoscopy (WLE). Recently high-resolution (HR) endoscopy enables us to visualize esophageal mucosa but resolution for glandular structures and cells is still low. Probe-based confocal laser endomicroscopy is a new promising diagnostic technique by which details of glandular and vascular structures of mucosal layer can be observed. However, the clinical utility of this new diagnostic tool has not yet been fully explored in a clinical setting.

Although there are a variety of advanced imaging modalities for Barrett's esophagus in development, there are few studies directly comparing these modalities. Leggett, et al. (2016) compared probe-based confocal endomicroscopy with volumetric endomicroscopy in ex vivo endoscopic mucosal resection specimens. The sensitivity, specificity, and diagnostic accuracy of probe-based confocal endomicroscopy for detection of BE dysplasia was 76% (95% confidence interval [CI], 59-88), 79% (95% CI, 53-92), and 77% (95% CI, 72-82), respectively. The use of volumetric laser endoscopy using a new algorithm showed a sensitivity of 86% (95% CI, 69-96), specificity of 88% (95% CI, 60-99), and diagnostic accuracy of 87% (95% CI, 86-88).

Guidelines from the Society for Thoracic Surgeons (Fernando, et al., 2009) state: "Advanced endoscopic imaging technologies, such as narrow-band imaging, auto-fluorescence, and confocal laser endo-microscopy have been used in attempts to improve detection of dysplasia."
Another approach is the use of vital stains, such as methylene blue, acetic acid, or indigo carmine, which can help direct and reduce the number of biopsies required to detect HGD with a segment of Barrett’s. These promising modalities have not currently demonstrated superiority to existing biopsy protocols.

Guidelines on management of BE from the American Gastroenterological Association (2011) state: "For the routine endoscopic evaluation of Barrett’s esophagus, the use of chromoendoscopy or electronic chromoendoscopy or advanced imaging techniques such as confocal laser endomicroscopy is not necessary. These technologies may be helpful in guiding the performance of biopsies in patients who are known to have dysplasia and in patients who have mucosal irregularities detected by white light endoscopy. Quality of Evidence: Low."

Guidelines on the role of endoscopy in Barrett’s esophagus and other premalignant conditions of the esophagus from the American Society for Gastrointestinal Endoscopy (2012) state: “Adjuncts to white-light endoscopy used to improve the sensitivity for the detection of BE and dysplastic BE include chromoendoscopy, electrical enhanced imaging, magnification, and confocal endoscopy. These techniques are still in development and are discussed in detail elsewhere.” An ASGE guideline on upper endoscopic surveillance (Hirota, et al., 2011) states: "The use of chromoendoscopy and enhanced endoscopic imaging to highlight an area for targeted biopsies shows promise, but the results appear to be poorly reproducible."

Guidelines from the Danish Society of Gastroenterology and Hepatology (Bremholm et al, 2012) state: "There is at present no evidence that routine use of chromoendoscopy or narrow band imaging (NBI), neither for diagnosis nor biopsy guidance, increases the number of or the precision of diagnostic findings. However, improved endoscopic image modalities (High Definition Endoscopy, Zoom-technique and NBI) is likely to improve the identification of dysplasia, and may possibly be used in targeting biopsies in follow-up endoscopies of BE."

A consensus statement (2012) concluded, based on "very low" quality evidence: "For evaluation of patients with BE, the use of high-resolution endoscopes and targeted biopsies of every suspicious lesion followed by 4-quadrant biopsies every 1–2 cm are recommended. Agreement: A 60 %, A 38 %, U 1 %, D 0 %, D 1 %. Evidence: Very low." The consensus statement explained: "A high-resolution endoscope (850,000 pixels) should be used to evaluate patients with BE. Standard-resolution endoscopes are not recommended, although there is scant scientific evidence for this recommendation. Evidence that greater resolution improves diagnosis is only available and supports narrow band imaging, but for chromoendoscopy there was no superiority to chromoendoscopy over standard endoscopy, although acetic acid spraying can
improve visualization of lesions. Even with high-resolution endoscopes, 4-quadrant biopsies are still necessary after careful evaluation of the BE segment to exclude synchronous neoplastic lesions."

Guidelines on BE from the British Society of Gastroenterology (Fitzgerald et al, 2014) state: "Other imaging techniques that have showed some value in Barrett’s oesophagus include confocal laser endomicroscopy, spectroscopy and optical coherence tomography; however, further studies are needed to clarify whether they can improve diagnostic accuracy during Barrett’s oesophagus surveillance."

Current guidelines on from Alberta Health Services (2014) on management of patients with early esophageal cancer, dysplastic and non-dysplastic Barrett’s esophagus make no recommendation for confocal laser endomicroscopy.

The French National Authority for Health (HAS, 2014) has initiated a review of endomicroscopic optical techniques for BE. The review protocol state that esophageal endomicroscopy does not replace histological examination. Histology provides the information necessary to diagnose and characterize lesions, and the depth of viewing of endomicroscopy is insufficient to assess invasion and thus guide treatment modalities (endoscopic or surgical). The HAS noted that the use of endomicroscopy could be justified with the development of endoscopic treatment of neoplastic lesions localized to the mucosa. The forthcoming HAS review will focus on this issue.

An American Gastroentrological Association White Paper (Sharma, et al., 2015) summarized the opinions of participants in a two-day workshop on endoscopic imaging-enhancing technologies. The workshop summary stated that several enhanced imaging technologies are now available to endoscopists for the management of patients with Barrett’s esophagus. Narrow-band imaging and confocal laser endoscopy have reached preservation and incorporation of valuable endoscopic innovation (PIVI) thresholds for eliminating random biopsies during BE surveillance in some studies at referral centers. The workshop summary stated, however, that these techniques ideally need to be validated in larger cohorts and in nonacademic centers. "As it stands today, detailed endoscopic examination with [high-definition white-light endoscopy] HDWLE and random 4-quadrant biopsy remains the standard of care." However, the workshop panelists agreed that in the hands of endoscopists who have met the PIVI thresholds with specific enhanced imaging techniques, use of the technique in BE patients is appropriate. The workshop summary stated that quality metrics (such as the BE inspection time) need to be developed and adopted for BE examination to ensure that BE patients receive high-quality endoscopic examinations.
The Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI) initiative implemented by the American Society of Gastrointestinal Endoscopy (ASGE) recommends that, before replacing the current Seattle protocol, a targeted imaging technique should have a per patient sensitivity of at least 90%, an NPV of at least 98%, and a specificity of at least 80% in the detection of high-grade dysplasia or early adenocarcinoma. A systematic evidence review by the American Society for Gastrointestinal Endoscopy found that that targeted biopsies with acetic acid chromoendoscopy, electronic chromoendoscopy by using narrow-band imaging, and endoscope-based CLE meet the thresholds set by the ASGE PIVI, at least when performed by endoscopists with expertise in advanced imaging techniques. The ASGE Technology Committee endorsed nonpreferentially using any of these advanced imaging modalities to guide targeted biopsies for the detection of dysplasia during surveillance of patients with previously nondysplastic BE, thereby replacing the currently used random biopsy protocols.

A meta-analysis by Fugazza et al (2016) of confocal laser endomicroscopy for gastrointestinal and pancreobiliary diseases demonstrated that confocal laser endoscopy yields a “per biopsy” pooled sensitivity of 58% and a pooled specificity of 90%, which was slightly increased to 79% sensitivity in the “per patient” analysis. The authors concluded, therefore, based on the PIVI initiative requirements, using CLE for the surveillance of BE does not appear to be sensitive enough to replace the Seattle biopsy protocol. The authors noted, however, that a recent multicenter RCT showed that combining CLE with high-definition WLE surpassed the PIVI threshold, with a per patient sensitivity of 95%, an NPV of 98% and a specificity of 92% [citing Canto, et al., 2014)]. The authors state that this study suggests that the combined use of CLE with high-definition WLE or NBI may be considered a valuable diagnostic tool for premalignant and malignant lesions. The authors concluded "[n]evertheless, prospective medicoeconomic studies have yet to be conducted."

American College of Gastroentrology guidelines on BE (Shaheen et al, 2016) state that "A wide variety of other image enhancement techniques have been studied including methylene blue staining, acetic acid staining, indigo carmine staining, autofluorescence endoscopy, confocal laser endomicroscopy, volumetric laser endomicroscopy, spectroscopy, and molecular imaging, but none of these methods appear ready for widespread clinical use at present."

Gastrectomy

UpToDate reviews on “Management of Barrett's esophagus” (Spechler, 2015) and “Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection” (Bergman, 2015) do not mention gastrectomy as a management tool.

Bariatric Surgery
In a prospective study, Braghetto et al (2012) evaluated the post-operative results after 3 different procedures -- (i) calibrated fundoplication + posterior gastropexy (CFPG), (ii) fundoplication + vagotomy + distal gastrectomy + Roux-en-Y gastrojejunostomy (FVDGYGJ), and (iii) laparoscopic resectional Roux-en-Y gastric bypass (LRRYGBP) -- among obese patients with BE (n = 139). In patients with short-segment BE (SSBE) who submitted to CFPG, the persistence of reflux symptoms and endoscopic erosive esophagitis was observed in 15 % and 20.2 % of them, respectively. Patients with long-segment BE (LSBE) were submitted to FVDGYGJ or LRRYGBP, which significantly improved their symptoms and erosive esophagitis. No modifications of lower esophageal sphincter pressure (LESP) were observed in patients who submitted to LRRYGBP before or after the operation. Acid reflux diminished after the 3 types of surgery were employed. Patients who submitted to LRRYGBP presented a significant reduction of body mass index (BMI) from 41.5 ± 4.3 to 25.7 ± 1.3 kg/m(2) after 12 months. The authors concluded that among patients with LSBE, FVDGYGJ presented very good results in terms of improving GERD and BE, but the reduction of weight was limited; LRRYGBP improved GERD disease and BE with proven reduction in body weight and BMI, thus becoming the procedure of choice for obese patients. These findings are promising, but they need to be validated by additional studies.

Furthermore, the ACG’ clinical guideline on “Diagnosis and management of Barrett's esophagus” (Shaheen et al, 2016) does not mention bariatric surgery as a therapeutic option.

Biomarker Panels

Eluri and colleagues (2015) noted that risk stratification in BE is challenging. These investigators evaluated the ability of a panel of genetic markers to predict progression to HGD or EAC. In this case-control study, these researchers assessed a measure of genetic instability, the mutational load (ML), in predicting progression to HGD or EAC. Cases had non-dysplastic BE or LGD at baseline and developed HGD/EAC greater than or equal to 1 year later. Controls were matched 2:1, had non-dysplastic BE or LGD, and no progression at follow-up. Formalin-fixed, paraffin-embedded tissue was micro-dissected for the epithelium. Loss of heterozygosity (LOH) and microsatellite instability (MSI) were assessed; ML was calculated from derangements in 10 genomic loci. High-clonality LOH mutations were assigned a value of 1, low-clonality mutations were assigned a value of 0.5, and MSI 0.75 at the first loci, and 0.5 for additional loci. These values were summed to the ML. Receiver operator characteristic (ROC) curves were created. There were 69 patients (46 controls and 23 cases). Groups were similar in age, follow-up time, baseline histology, and the number of micro-dissected targets. Mean ML in pre-progression biopsies was higher in cases (2.21) than in controls (0.42; p < 0.0001). Sensitivity was 100 % at ML greater than or equal to 0.5 and specificity was 96 % at ML greater than or equal to 1.5. Accuracy was highest at 89.9 % for ML greater than or equal to 1; ROC curves for ML greater
than or equal to 1 demonstrated an area under the curve (AUC) of 0.95. The authors concluded that ML in pre-progression BE tissue predicted progression to HGD or EAC. Moreover, they stated that although further validation is needed, ML may have utility as a biomarker in endoscopic surveillance of BE.

Findlay et al (2016) stated that BE is a common and important precursor lesion of EAC; 1/3 of patients with BE are asymptomatic, and the ability to predict the risk of progression of metaplasia to dysplasia and EAC (and therefore guide management) is limited. There is an urgent need for clinically useful biomarkers of susceptibility to both BE and risk of subsequent progression. These researches identified, reviewed, and meta-analyzed genetic biomarkers reported to predict both. A systematic review of the PubMed and Embase databases was performed in May 2014. Study and evidence quality were appraised using the revised American Society of Clinical Oncology guidelines, and modified Recommendations for Tumor Marker Scores. Meta-analysis was performed for all markers assessed by more than 1 study. A total of 251 full-text articles were reviewed; 52 were included. A total of 33 germline markers of susceptibility were identified (level of evidence II to III); 17 were included; 5 somatic markers of progression were identified; meta-analysis demonstrated significant associations for chromosomal instability (level of evidence II). One somatic marker of progression/relapse following photodynamic therapy was identified. However, a number of failings of methodology and reporting were identified. This was the first systematic review and meta-analysis to evaluate genetic biomarkers of BE susceptibility and risk of progression. The authors concluded that while a number of limitations of study quality tempered the utility of those markers identified, some-in particular, those identified by genome-wide association studies, and chromosomal instability for progression-appear plausible, although robust validation is needed. Moreover, these researchers stated that the overall evidence base was characterized by widespread methodological issues, which limited the immediate clinical utility of these markers. They stated that larger studies with more robust design are needed to validate these markers, identify novel variants, and incorporate them into clinical practice.

The ACG updated its guidance for the best practices in caring for patients with BE (Shaheen et al, 2016). These guidelines continue to endorse screening of high-risk patients for BE; however, routine screening is limited to men with reflux symptoms and multiple other risk factors. Acknowledging recent data on the low risk of malignant progression in patients with non-dysplastic BE, endoscopic surveillance intervals are attenuated in this population; patients with non-dysplastic BE should undergo endoscopic surveillance no more frequently than every 3 to 5 years. Neither routine use of biomarker panels nor advanced endoscopic imaging techniques (beyond high-definition endoscopy) is recommended at this time. Endoscopic ablative therapy is recommended for patients with BE and HGD, as well as T1a EAC. Based on recent level 1 evidence, endoscopic ablative therapy is also recommended for patients with BE and LGD,
although endoscopic surveillance continues to be an acceptable alternative. Given the relatively common recurrence of BE after ablation, the guidelines suggested post-ablation endoscopic surveillance intervals. The authors noted that although many of the recommendations provided were based on weak evidence or expert opinion, this document provided a pragmatic framework for the care of the patient with BE.

Measurements of Serum Levels of Adipokines and Insulin

Chandar et al (2015) stated that metabolically active visceral fat may be associated with esophageal inflammation, metaplasia, and neoplasia. These researchers performed a meta-analysis to evaluate the association of serum adipokines and insulin with BE. They performed a systematic search of multiple electronic databases, through April 2015, to identify all studies reporting associations between leptin, adiponectin, insulin, insulin resistance, and risk of BE in adults. Comparing the highest study-specific category with the reference category for each hormone, these investigators estimated the summary adjusted odds ratio (aOR) and 95 % CI, using a random effects model. They identified 9 observational studies (10 independent cohorts; 1,432 patients with BE total, and 3,550 control subjects). Meta-analysis revealed that high serum level of leptin was associated with 2-fold higher risk of BE (BE cases versus population control subjects in 5 studies: aOR, 2.23; 95 % CI: 1.31 to 3.78; I(2), 59 %). Total serum level of adiponectin was not associated with BE (BE cases versus population control subjects in 5 studies: aOR, 0.79; 95 % CI: 0.46 to 1.34; I(2), 65 %), although 1 study observed decreased risk of BE with increased level of low-molecular-weight adiponectin. High serum level of insulin was associated with increased risk of BE (BE cases versus population control subjects in 3 studies: aOR, 1.74; 95 % CI: 1.14 to 2.65; I(2), 0), whereas insulin resistance was not associated with increased risk of BE (BE cases versus GERD control subjects in 2 studies: aOR, 0.98; 95 % CI: 0.42 to 2.30; I(2), 64 %). The authors concluded that increased serum levels of leptin and insulin are associated with increased risk of BE, compared with population control subjects. In contrast, increased total serum levels of adiponectin and insulin do not seem to modify BE risk. They stated that well-designed longitudinal studies of incident BE are needed to clarify existing associations of serum adipokines and insulin with BE.

SOX2 Expression Testing for Prediction of Neoplastic Progression in BE

van Olphen et al (2015) evaluated the predictive value (PV) of SOX2 expression for neoplastic progression in BE patients. These researchers conducted a case-control study within a prospective cohort of 720 BE patients. Patients with neoplastic progression, defined as the development of HGD or EAC, were classified as cases and patients without neoplastic progression were classified as controls. SOX2 expression was determined by immunohistochemistry in more than 12,000 biopsies from 635 patients; these results were
combined with the authors’ previous p53 immunohistochemical data. Non-dysplastic BE showed homogeneous nuclear staining for SOX2, whereas SOX2 was progressively lost in dysplastic BE. Loss of SOX2 was seen in only 2 % of biopsy series without dysplasia, in contrast to 28 % in LGD and 67 % in HGD/EAC. Loss of SOX2 expression was associated with an increased risk of neoplastic progression in BE patients after adjusting for gender, age, BE length, and esophagitis (adjusted relative risk 4.8; 95 % CI: 3.2 to 7.0). The positive PV for neoplastic progression increased from 16 % with LGD alone to 56 % with concurrent loss of SOX2 and aberrant p53 expression. The authors concluded that SOX2 expression is lost during transition from non-dysplastic BE to HGD/EAC, and it is associated with an increased risk of neoplastic progression. The highest PV is achieved by concurrent loss of SOX2 and aberrant p53 expression in BE patients with LGD. They stated that the use of these markers has the potential to significantly improve risk stratification of Barrett surveillance.

Markers of Intestinal Phenotype, Mucin Glycoprotein Immunostains, and p53

Srivastava and colleagues (2017) noted that BE is a known risk factor for the development of esophageal adenocarcinoma. Pathologists play a critical role in confirming the diagnosis of BE and BE-associated dysplasia. As these diagnoses are not always straight-forward on routine hematoxylin and eosin-stained slides, numerous ancillary stains have been used in an attempt to help pathologists confirm the diagnosis. On the basis of an in-depth review of the literature, the Rodger C. Haggitt Gastrointestinal Pathology Society provided recommendations regarding the use of ancillary stains in the diagnosis of BE and BE-associated dysplasia. The authors stated that because goblet cells are almost always identifiable on routine hematoxylin and eosin-stained sections, there is insufficient evidence to justify reflexive use of Alcian blue (at pH 2.5) and/or periodic-acid Schiff stains on all esophageal biopsies to diagnose BE. In addition, the use of mucin glycoprotein immunostains and markers of intestinal phenotype (CDX2, Das-1, villin, Hep Par 1, and SOX9) are not indicated to aid in the diagnosis of BE at this time. A diagnosis of dysplasia in BE remains a morphologic diagnosis, and hence, ancillary stains are not recommended for diagnosing dysplasia. Although p53 is a promising marker for identifying high-risk BE patients, it is not recommended for routine use at present; additional studies are needed to address questions regarding case selection, interpretation, integration with morphologic diagnosis, and impact on clinical outcome.

Cryotherapy for Persistent Barrett’s Esophagus after Radiofrequency Ablation

Visrodia and colleagues (2018) stated that a small but significant proportion of patients with BE have persistent dysplasia or IM after treatment with RFA. These investigators examined the efficacy of 2nd-line cryotherapy in patients with BE who have persistent dysplasia or IM after RFA by conducting a systematic review and meta-analysis. They performed a systematic
literature search of PubMed, Embase, and Web of Science through September 1, 2017. Articles were included for meta-analysis based on the following inclusion criteria: greater than or equal to 5 patients with BE treated with RFA had persistent dysplasia or IM; they subsequently underwent greater than or equal to 1 session of cryotherapy with follow-up endoscopy; the proportions of patients achieving complete eradication of dysplasia (CE-D) and/or IM (CE-IM) were reported. The main outcomes were pooled proportions of CE-D and CE-IM by using a random effects model. A total of 11 studies making up 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA were included. The pooled proportion of CE-D was 76.0 % (95 % CI: 57.7 to 88.0), with substantial heterogeneity ($I^2 = 62 \%$). The pooled proportion of CE-IM was 45.9 % (95 % CI: 32.0 to 60.5) with moderate heterogeneity ($I^2 = 57 \%$). Multiple pre-planned sub-group analyses did not sufficiently explain the heterogeneity; adverse effects were reported in 6.7 % of patients. The authors concluded that cryotherapy successfully achieved CE-D in 3/4 and CE-IM in 50 % of patients with BE who did not respond to initial RFA. They stated that considering its favorable safety profile, cryotherapy may be a viable 2nd-line option for this therapeutically challenging cohort of patients with BE, however, higher-quality studies are needed to validate these findings.

The authors stated that this meta-analysis had several potential limitations. All included studies were relatively small and observational, and most studies were single-center series published in abstract form alone, amounting to a limited set of data from which these investigators derived the earlier conclusions. This was not surprising given that the vast majority of patients would respond to RFA. Because there is no uniformly accepted definition for RFA-refractory BE, criteria for proceeding to cryotherapy varied among institutions. However, 5 studies had a reported minimum number of RFA sessions, and most studies reported a mean-median 2 to 3 RFA sessions before cryotherapy was initiated. These researchers recognized that it is not uncommon for patients to require greater than 2 to 3 RFA sessions to achieve CE-D or CE-IM, and so switching to a 2nd-line therapy at this juncture may be considered premature. However, these investigators suspected this was done in select patients who had a very poor initial response to RFA, and additional RFA was deemed low yield, but they could not be sure. Furthermore, long-term follow-up was not reported in the majority of studies, limiting conclusions regarding the risk of recurrence or progression in this seemingly higher risk cohort. The authors encountered moderate-to-substantial heterogeneity that could not be explained by several pre-planned subgroup analyses. However, such heterogeneity was not uncommon in studies of prevalence and/or proportion, and conceptually the studies were similar based on the strict inclusion and exclusion criteria.

Mohan and colleagues (2019) noted that RFA is the preferred therapeutic option for BE to achieve CE-D, and CE-IM. Cryotherapy, using liquid nitrogen (LNC), is a cold-induced tissue-injury technique option for the ablation of BE. These investigators performed a systematic
review and meta-analysis to evaluate the overall safety and efficacy of LNC in the treatment of BE. They carried out a search of multiple electronic databases and conference proceedings from inception through June 2018. The primary outcome was to estimate the pooled rates of CE-IM, CE-D, and CE-HGD. The secondary outcome was to estimate the risk of adverse events (AEs) and recurrence of disease following LNC. A total of 9 studies reported 386 patients who were treated with LNC. The pooled rate of CE-IM was 56.5 % (95 % CI: 48.5 to 64.2, I² = 47), pooled rate of CE-D was 83.5 % (95 % CI: 78.3 to 87.7, I² = 22.8), and pooled rate of CE-HGD was 86.5 % (95 % CI: 64.4 to 95.8, I² = 88.1). Rate of AEs was 4.7 %, and the risk of BE recurrence was 12.7 %. On subgroup analysis, the pooled rate of CE-IM with LNC in patients who failed RFA was 58.4 % (95 % CI: 47.2 to 68.8, I² = 32.5), and the pooled rate of CE-D in the same population was 81.9 % (95 % CI: 72.5 to 88.6, I² = 5.9). CE-D rates with LNC were comparable to RFA while CE-IM rates appeared to be lower than the rates achievable with RFA; CE-IM rate in RFA failed patients was 58.4 %. The authors concluded that LNC was a rescue option to consider in RFA-failed BE patients. At this time, data are lacking to say if LNC is inferior or superior to RFA in treatment-naive patients. The quality of available data is weak with regards to cryotherapy as compared to RFA in treatment-naive patients. Hence with current available data, cryotherapy cannot be recommended as 1st-line treatment in BE. Novel methods of cryogen delivery, like the nitrous-oxide cryo-balloon are promising and may soon make cryotherapy as acceptable 1st-line treatment in BE. These researchers stated that more prospective, well-conducted randomized studies are needed to answer this question.

The authors stated that this review/meta-analysis had several limitations. The included studies were not entirely representative of the general population and community practice, with most studies being retrospective and performed in tertiary-care referral centers. They did not include a comparator-group in their analysis against LNC. These investigators were unable to identify a high-risk subset of patients undergoing the procedure who were likely to experience success, with minimal risk to AEs. These researchers could not examine the influence of nodular-BE, and BE-length on the reported outcomes. Patient related characteristics such as age, smoking, previous attempts and procedures, need to be accounted for in identifying this high-risk subset that may benefit from LNC in the treatment of BE.

Hamade and co-workers (2019) carried out a systematic review to examine the efficacy of cryotherapy as the primary treatment of BE. An electronic database search was performed (PubMed, Embase, Cochrane, and Google Scholar) to search for studies with cryotherapy as the initial primary modality of ablation in patients with BE neoplasia. Studies that included patients with other prior forms of therapy were excluded. The primary outcomes were the pooled rates of CE-IM and CE of neoplasia (CE-N). Secondary outcomes were recurrence rates of neoplasia and IM and AEs. The statistical software OpenMetaAnalyst was used for analysis with pooled estimates reported as proportions (%) with 95 % CI with heterogeneity (I²) among studies. The
search revealed 6 eligible studies with a total of 282 patients (91.5 % men, average age of 65.3 years) with 459 person years of follow-up; 69.35 % [95 % CI: 52.1 % to 86.5 %]) of patients achieved CE-IM and 97.9 % (95 % CI: 95.5 % to 100 %) had CE-N; 7.3 % of patients had persistent dysplasia with 4 % progressing to cancer. The recurrence rate of neoplasia was 10.4 and that of IM was 19.1 per 100 patient years of follow-up. The overall rate of stricture formation was 4.9 %. There were scarce data on the use of cryotherapy as the primary modality for the treatment of BE dysplasia. The published data demonstrated efficacy rates of 69 % and 98 % for CE-IM and CE-N, respectively. The authors concluded that these results need to be evaluated in prospective, comparative trials with other forms of therapy.

Use of miRNA Biomarkers of Barrett's Esophagus

Clark and colleagues (2018) stated that esophageal adenocarcinoma (EAC) is a highly aggressive malignancy that develops from BE. MicroRNAs (miRNAs), short non-coding regulatory RNAs, are frequently dysregulated in BE and are thought to play key roles in the onset of BE and its progression to EAC; thus, miRNAs have potential diagnostic and prognostic value and are increasingly being used as cancer biomarkers. In a systematic review, these investigators summarized the current literature related to miRNAs that are dysregulated in BE within the context of Hedgehog, Notch, MAPK, NF kappa-B, Wnt and epithelial-mesenchymal transition (EMT) signaling, which are thought to drive BE onset and progression. This comprehensive analysis of miRNAs and their associated signaling in the regulation of BE provided an overview of vital discoveries in this field and highlighted gaps in the understanding of BE pathophysiology that warrant further investigation. The authors concluded that identification of clinically reliable early miRNA biomarkers of BE will require extensive validation and a deeper understanding of the cellular signaling events that drive BE development. Of the miRNAs discussed, it remains unclear which miRNAs have the potential to serve as biomarkers specific to BE and which are broad spectrum cancer biomarkers. They stated that further studies into the mechanisms by which circulating miRNAs become differentially expressed are needed to identify those miRNAs of real clinical importance. A number of technical challenges remain that have hindered current efforts at identifying miRNA biomarkers including low miRNA yield from serum samples, lack of suitable endogenous miRNA controls, and a lack of strategies to deal with normal variation in circulating miRNA levels. These researchers noted that improved early detection of BE and other cancers will only occur by overcoming these technical challenges and by obtaining a more detailed understanding of miRNA signaling network.

Barrett's Esophagus Fluorescence In Situ Hybridization (FISH) Assay (e.g., MolDX)
According to Acupath Laboratories (2018), the Barrett’s esophagus FISH assay utilizes esophageal brushings, collected in conjunction with biopsies, to identify genetic abnormalities that enable the clinician to risk stratify patients into high and low risk groups. The test provides objective information to use when determining the aggressiveness of treatment and addresses several important deficiencies of current biopsy methodology including sampling error, the time required to collect the recommended # of biopsies, and inter-observer variability.

Rossi et al (2006) noted that Her-2/neu is a proto-oncopogene frequently over-expressed in breast cancer, recently found to be also over-expressed in carcinoma arising on BE. Immunohistochemistry and FISH are conventionally used for Her-2 testing in carcinomas, but a single assay is not yet accepted as a "gold standard" in BE. These investigators evaluated the correlation between histopathology variables and gene expression/amplification in the sequence BE-low grade dysplasia (LGD)-high grade dysplasia (HGD)-adenocarcinoma. A total of 50 esophageal specimens from patients with a diagnosis of BE (21 BE, 4 LGD, 12 HGD, and 13 adenocarcinomas) were evaluated. Histopathologic evaluation was carried out using hematoxylin and eosin staining. Paraffin-embedded tissues were investigated for Her-2 by immunohistochemistry (HercepTest) and FISH. HercepTest was scored 0, 1+, 2+, and 3+ depending on the percentage (cut-off 10 %) of membrane staining, whereas gene assessment evaluated by FISH was based on the ratio between Her-2/neu and the 17 chromosome copy number. There was a positive correlation between gene amplification and protein over-expression. No case with HercepTest scoring 0 or 1+ displayed gene amplification, but this was present in 20 % of cases scoring 2+ and in all cases scoring 3+. Her-2/neu amplification or over-expression was never observed in BE. Gene amplification and over-expression was observed in more than 50 % of dysplasias and adenocarcinomas. The authors concluded that Her-2/neu amplification/over-expression might be considered as a marker of progression from BE to dysplasia; FISH may represent a useful diagnostic tool to integrate the result of HercepTest for selecting patients for more targeted therapeutic approaches.

Rygiel et al (2007) stated that automated assessment of genetic abnormalities detected by FISH in brush cytology specimens from patients with BE may enhance the clinical applicability of this methodology. These researchers attempted to validate a novel, automated, proprietary system (CytoVison SPOT AX) for the assessment of FISH abnormalities in BE brush cytology and, subsequently used this automated method for screening of a BE surveillance cohort. FISH with DNA probes for chromosomes 9, 17, and Y, and for the 9p21 (p16), 17q11.2 (Her2/neu), and 17p13.1 (p53) loci was applied on brush cytology specimens from a surveillance cohort of 151 patients with BE. Validation of the automated system was performed by comparison of the automated FISH results with manual scores for the first 60 patients. There was 98 % concordance between manual and automated FISH analysis with kappa values from 0.49 to 1 for the different probes. The loss of 17p13.1 (p53) was observed in only 5 % of patients with no
dysplasia (ND) and in 9% of patients with LGD but increased to 46% in patients with HGD (p < 0.005; Fisher exact test). Chromosomes 9 and 17 were observed in 6% of patients with ND, in 21% of patients with LGD, and in 62% of patients with HGD (p < 0.05); 10% of patients with ND had loss of the Y chromosome, which increased to 27% in patients with HGD (p < 0.05). The amplification of 17q11.2 (Her2/neu) was detected in 62% of patients with HGD (p < 0.001).

The authors concluded that the findings of this study indicated that the CytoVision SPOT AX is an objective, efficient system for the analysis of DNA-FISH on BE brush cytology and is applicable for analyzing large populations of BE patients. In the current study cohort, the loss of 17p13.1 (p53), Y chromosome loss, and polysomy of chromosomes 17 and 9 were correlated with increasing grade of dysplasia in patients with BE. Moreover, these researchers stated that future follow-up of the surveillance cohort are needed to prove the true predictive value of these abnormalities. They believed that the potential of automated FISH analysis for the accurate assessment of important genetic changes can improve the effectiveness of future surveillance programs.

Fritcher et al (2008) stated that new detection methods with prognostic power are needed for early identification of dysplasia and EA in patients with BE. These investigators evaluated the relative sensitivity and specificity of conventional cytology, DNA ploidy analysis with digital image analysis (DIA), and FISH for the detection of dysplasia and adenocarcinoma in endoscopic brushing specimens from 92 patients undergoing endoscopic surveillance for BE. FISH used probes to 8q24 (C-MYC), 9p21 (P16), 17q12 (HER2), and 20q13; 4-quadrant biopsies taken every centimeter throughout visible Barrett's mucosa were used as the gold standard. The sensitivity of cytology, DIA, and FISH for LGD was 5%, 5%, and 50%, respectively; for HGD, 32%, 45%, and 82%, respectively; and for EA, 45%, 45%, and 100%, respectively. FISH was more sensitive (p < 0.05) than cytology and DIA for LGD, HGD, and EA. The specificity of cytology, DIA, and FISH among patients (n = 14) with tissue showing only benign squamous mucosa was 93%, 86%, and 100% (p = 0.22), respectively. All patients with a polysomic FISH result had HGD and/or EA within 6 months (n = 33). There was a significant difference between FISH categories (negative, 9p21 loss, gain of a single locus, and polysomy) for progression to HGD/EA (p < 0.001). The authors concluded that these findings suggested that FISH has high sensitivity for the detection of dysplasia and EA in BE patients, with the power to stratify patients by FISH abnormality for progression to HGD/EA. Moreover, they stated that further studies in a general population are needed to determine the appropriate use of FISH results in clinical practice. The authors noted that the main drawback of this study was that there were few patients with a histologic diagnosis of benign squamous epithelium (n = 14) at the time of the brushing because of the high prevalence of disease in this population. This limitation may explain the fact that the specificity of “Cytology P + S + A” was unexpectedly the same as the specificity of “Cytology P + S”.

www.aetna.com/cpb/medical/data/700_799/0728.html
Brankley et al (2012) noted that the progression of intestinal metaplasia to EA in patients with BE is partly driven by chromosomal alterations that activate oncogenes and inactivate tumor suppressor genes. These researchers determined how alterations of 4 frequently affected genes correlate with the range of histopathologic lesions observed in resected esophagi of patients with BE; FISH was used to assess 83 tissue sections from 10 BE esophago-gastrectomy specimens for chromosomal alterations of 8q24 (MYC), 9p21 (CDKN2A; alias P16), 17q12 (ERBB2), and 20q13.2 (ZNF217). Histologic lesions assessed included gastric metaplasia (n = 8), intestinal metaplasia (n = 43), low-grade dysplasia (n = 28), high-grade dysplasia (n = 25), and adenocarcinoma (n = 16). Histologic maps showing the correlation between fluorescence in situ hybridization abnormalities and corresponding histology were created for all patients. Chromosomal abnormalities included 9p21 loss, single locus gain, and polysomy. A greater number of chromosomal alterations were detected as the severity of histologic diagnosis increased from intestinal metaplasia to adenocarcinoma. All patients had alterations involving the CDKN2A gene. CDKN2A loss was the only abnormality detected in 20 (47 %) of 43 areas of intestinal metaplasia. Polysomy, the most common abnormality in dysplastic epithelium and adenocarcinoma, was observed in 16 (57 %) of 28 LGD, 22 (88 %) of 25 HGD, and 16 (100 %) of 16 adenocarcinoma. The authors concluded that the findings of this study improved the understanding of the role that chromosomal instability and alterations of tumor suppressor genes such as CDKN2A and oncogenes such as ERBB2 play in the progression of intestinal metaplasia to adenocarcinoma in patients with BE. These preliminary findings need to be validated by well-designed studies.

Brankley et al (2016) stated that BE with HGD defines a group of individuals at high risk of progression to EA; and FISH has been shown to be useful for the detection of dysplasia and EA in endoscopic brushing specimens from BE patients. These researchers examined if FISH in combination with histological findings would further identify more rapid progressors to EA. This is a retrospective cohort study of high-risk patients, having a history of biopsy-confirmed HGD without EA, with an endoscopic brushing specimen analyzed by FISH while undergoing endoscopic surveillance and treatment between April 2003 and October 2010. Brushing specimens were assessed by FISH probes targeting 8q24 (MYC), 9p21 (CDKN2A), 17q12 (ERBB2), and 20q13 (ZNF217) and evaluated for the presence of polysomy, defined as multiple chromosomal gains (displaying greater than or equal to 3 signals for greater than or equal to 2 probes). Specimens containing greater than or equal to 4 cells exhibiting polysomy were considered polysomic. HGD was confirmed by at least 2 experienced gastro-intestinal pathologists. Of 245 patients in this study, 93 (38.0 %) had a polysomic FISH result and 152 (62.0 %) had a non-polysomic FISH result. Median follow-up was 3.6 years (interquartile range [IQR] 2 to 5 years). Patients with a polysomic FISH result had a significantly higher risk of developing EA within 2 years (14.2 %) compared with patients with a non-polysomic FISH result (1.4 %, p < 0.001). The authors concluded that these findings suggested that a polysomic FISH
result in BE patients with simultaneous HGD identified patients at a higher risk for developing EA compared with those with non-polysomy. Moreover, they stated that additional multi-institutional prospective studies are needed to confirm the findings of this study and to address the role of FISH analysis in predicting risk of progression to EA in a lower-risk BE population, including patients with LGD and non-dysplastic BE.

The ACG’s clinical guideline on “Diagnosis and management of Barrett’s esophagus” (Shaheen et al, 2016) does not mention FISH as a management tool.

Poneros et al (2017) noted that preliminary single-institution data suggested that FISH may be useful for detecting HGD and EA in patients with BE. This multi-center study aimed to validate the measurement of polysomy (gain of at least 2 loci) by FISH as a way to discriminate degrees of dysplasia in BE specimens. Tissue specimens were collected from 4 different hospitals and read by both the local pathology department (“Site diagnosis”) and a single central pathologist (“Review diagnosis”) at a separate institution. The specimens then underwent FISH analysis using probes 8q24 (MYC), 9p21 (CDKN2A), 17q12 (ERBB2), and 20q13 (ZNF217) for comparison. A total of 46 non-BE, 42 non-dysplastic specialized intestinal metaplasia (SIM), 23 indefinite-grade dysplasia (IGD), 10 LGD, 29 HGD, and 42 EA specimens were analyzed. These investigators found that polysomy, as detected by FISH, was the predominant chromosomal abnormality present as dysplasia increased. Polysomy was also the best predictor for the presence of dysplasia or EA when comparing its area under the curve to that of other FISH abnormalities. These investigators observed that if at least 10 % of cells had polysomy within a specimen, the FISH probe was able to differentiate between EA/HGD and the remaining pathologies with a sensitivity of 80 % and a specificity of 88 %. The authors concluded that the findings of this study demonstrated that using FISH to determine the percentage of cells with polysomy can accurately and objectively aid in the diagnosis of HGD/EA in BE specimens. These findings need to be further investigated in well-designed studies.

Furthermore, UpToDate reviews on “Barrett’s esophagus: Surveillance and management” (Spechler, 2018a) and “Barrett’s esophagus: Epidemiology, clinical manifestations, and diagnosis” (Spechler, 2018b) do not mention FISH/fluorescent in situ hybridization as a management tool.

Methylated DNA Markers for Detection of Barrett's Esophagus

Iyer and colleagues (2018) stated that minimally invasive methods have been described to detect BE, but are limited by subjectivity and suboptimal accuracy. These researchers identified methylated DNA markers (MDMs) for BE in tissue and assessed their accuracy on whole esophagus brushings and capsule sponge samples. Step 1: Unbiased whole methylome
sequencing was performed on DNA from BE and normal squamous esophagus (SE) tissue. Discriminant MDM candidates were validated on an independent patient cohort (62 BE cases, 30 controls) by quantitative methylation specific PCR (qMSP).

Step 2: Selected MDMs were further evaluated on whole esophageal brushings (49 BE cases, 36 controls); 35 previously sequenced EAC MDMs were also evaluated. Step 3: 20 BE cases and 20 controls were randomized to swallow capsules sponges (25 mm, 10 pores or 20 pores per inch (ppi)) followed endoscopy. DNA yield, tolerability, and mucosal injury were compared. Best MDM assays were performed on this cohort. Step 1: 19 MDMs with AUCs of greater than 0.85 were carried forward. Step 2: On whole esophageal brushings, 80 % of individual MDM candidates showed high accuracy for BE (AUCs: 0.84 to 0.94). Step 3: The capsule sponge was swallowed and withdrawn in 98 % of subjects. Tolerability was superior with the 10 ppi sponge with minimal mucosal injury and abundant DNA yield. A 2-marker panel (VAV3 + ZNF682) yielded excellent BE discrimination (AUC = 1). The authors concluded that identified MDMs discriminated BE with high accuracy; BE detection appeared safe and feasible with a capsule sponge. Moreover, they stated that corroboration in larger studies is needed.

Optical Coherence Tomography or Evaluation of Barrett's Esophagus

Kohli and colleagues (2017) stated that optical coherence tomography (OCT) can generate high-resolution images of the esophagus that allows cross-sectional visualization of esophageal wall layers. These researchers conducted a systematic review to assess the utility of OCT for diagnosing of esophageal IM, BE, dysplasia, cancer and staging of early esophageal cancer. English language human observational studies and clinical trials published in PubMed and Embase were included if they assessed any of the following: (i) in-vivo features and accuracy of OCT at diagnosing esophageal IM, sub-squamous intestinal metaplasia (SSIM), dysplasia, or cancer, and (ii) accuracy of OCT in staging esophageal cancer; 21 of the 2,068 retrieved citations met inclusion criteria. In the 2 prospective studies that assessed accuracy of OCT at identifying IM, sensitivity was 81 % to 97 %, and specificity was 57 % to 92 %. In the 2 prospective studies that assessed accuracy of OCT at identifying dysplasia and early cancer, sensitivity was 68 % to 83 %, and specificity was 75 % to 82 %. Observational studies described significant variability in the ability of OCT to accurately identify SSIM; 2 prospective studies that compared the accuracy of OCT at staging early squamous cell carcinoma (SCC) to histologic resection specimens reported accuracy of greater than 90 %. Risk of bias and applicability concerns was rated as low among the prospective studies using the QUADAS-2 questionnaire. The authors concluded that OCT may identify intestinal metaplasia and dysplasia, but its accuracy may not meet recommended thresholds to replace 4-quadrant biopsies in clinical practice. They stated that OCT may be more accurate than EUS at staging early esophageal cancer, but randomized trials and cost-effective analyses are lacking.
Cytosponge for Screening and Surveillance of Barrett’s Esophagus

Cytosponge is a mesh surrounded by gelatin capsule attached to a string that is passed trans-orally. Five minutes after swallowing, the capsule dissolves in the proximal stomach, expanding the mesh to a sphere of 3 cm. The sample containing cytological specimen is stained with Trefoil Factor3 (TFF3), which is a biomarker for IM. In addition to TFF3, Cytosponge sample can be used for detection of other additional biomarkers for BE such as TFPI2, TWIST1, ZNF345, and ZNF569, which can further improve the sensitivity.

Iqbal and colleagues (2018) noted that esophageal adenocarcinoma is an increasingly common cause of morbidity and mortality in developed countries. Most cases are considered the consequence of chronic GERD, with subsequent Barrett's metaplasia and dysplasia. Because progression from Barrett's metaplasia to cancer occurs over many years, endoscopic screening and surveillance programs have been established, albeit with little or no consideration for cost-effectiveness. As an alternative to the expensive and resource-demanding endoscopic surveillance, the Cytosponge has been developed to sample the esophageal mucosa efficiently. The device is a compressed mesh sponge encapsulated in an ingestible gelatin pill attached to a string. After swallowing, the capsule dissolves allowing the sponge to expand in the stomach. As it is pulled out, cells are collected from the esophagogastric junction and throughout the esophagus. The cellular samples can be analyzed by cytology, immunohistochemistry, and molecular markers. These researchers conducted a systematic review of all recent relevant studies to help define the role of this novel technology, including studies of screening and surveillance of BE, esophageal squamous dysplasia detection, detection of eosinophilic esophagitis, and evaluation of benign esophageal diseases. With the major limitation that most studies were performed by a single investigative group that developed the technology, the device yielded overall impressive results against the endoscopy/biopsy gold standard. Patient acceptability was high. The authors concluded that if these promising early findings are validated by other investigators in other populations, the Cytosponge represents an important new advance in the detection of esophageal pathology that could potentially decrease the burden of endoscopic esophageal sampling.

Januszewicz and associates (2019) stated that non-endoscopic methods for diagnosis and surveillance of BE and eosinophilic esophagitis are needed. Cytosponge is a minimally invasive device for esophageal cell sampling. These researchers evaluated the safety and acceptability of this device. They collected data from 5 prospective trials from patients with reflux disease, BE, or eosinophilic esophagitis in primary and secondary care. They analyzed data from 2,672 Cytosponge procedures, performed in 2,418 individuals from 2008 through 2017. Acceptability of the Cytosponge and subsequent endoscopy were calculated using the visual analogue scale (VAS; score of 0 for the lowest and 10 for highest level of acceptability) and compared using a
Mann Whitney test. The number of attempts, failures in swallowing the device, and occurrence of AEs were analyzed. Risk factors for failure in swallowing were analyzed using a multi-variate regression model. There were 2 AEs related to the device: a pharyngeal bleed and 1 case of detachment (less than 1:2000). The median acceptability score for Cytosponge was 6.0 (IQR, 5.0 to 8.0), which was higher than for endoscopy without sedation (median of 5.0, IQR, 3.0 to 7.0; p < 0.001) and lower than for endoscopy with sedation (median of 8.0, IQR, 5.0 to 9.0; p < 0.001). Nearly all patients (96.5 %) successfully swallowed the Cytosponge, most often on the 1st swallow attempt (90.1 %). Failure to swallow the device was more likely to occur in secondary care (OR, 5.13, 95 % CI: 1.48 to 17.79; p < 0.01). The authors concluded that in this first review of clinical data on safety and acceptability of the Cytosponge, they had demonstrated that this device has a favorable safety and acceptability profile. The relative ease of administration and the higher safety profile as compared to endoscopy made it a promising tool to be used in the primary care setting as a screening and surveillance test for esophageal disorders such as BE or eosinophilic esophagitis. Results from the ongoing BEST3 randomized trial will be critical prior to implementing the Cytosponge test for widespread use.

The authors stated that this study had several drawbacks. There were comparatively fewer acceptability scores recorded for endoscopy than the Cytosponge. This was because patients enrolled onto the BEST1 trial did not have the acceptability score recorded following endoscopy. Furthermore, the VAS scale was a crude measure of acceptability and further quantitative and qualitative interviews are needed to fully understand the patient experience. Some of the studies included in this analysis had more complex tools to measure patients’ experience, such as Impact Event Score or Spielberger state trait anxiety inventory, however these researchers did not include it in this analysis since they were not used across all the studies. Moreover, these researchers could not conclude whether the use of local anesthetic had any influence on the acceptability ratings of the Cytosponge test, as its use wasn’t routinely recorded and data were missing for nearly 50 % of the procedures.

Kaz and Grady (2019) stated that a major barrier to the identification of people with BE is that upper GI tract endoscopy is the only screening test available. Although safe and accurate, endoscopy is an inconvenient and expensive screening test, which has led to controversy regarding the population health value of BE screening programs. This has led to intense interest in the development of an inexpensive, safe and accurate BE screening test that is acceptable to patients. To this end, a variety of techniques are being developed that are less costly and less invasive than upper endoscopy and that could be deployed on a population level. The most mature and promising of these emerging assays are based on swallowable balloons or capsules that are tethered to a string or small tube that remains outside the patient’s mouth. After being swallowed, the string is used to retrieve the device and collect cellular material from the esophagus for analysis. Of the current devices, the EsophaCap and Cytosponge were the first
iterations of the swallowable cytology collection devices and consist of an expandable sponge. These investigators noted that to realize the potential impact of these emerging BE biomarker assays, larger prospective trials in targeted populations, such as the ongoing BEST3 study with the Cytosponge and clinical trials supported by the BETRNET, EDRN, and GI SPORE mechanisms, are needed to establish that these devices are safe, accurate, easy to administer, and cost-effective. If these studies show that swallowable device-based methods are effective and more people are screened for BE, issues related to over-diagnosis and over-treatment will need to be addressed, as will the need for non-endoscopic surveillance methods that are inexpensive, accurate and safe. There are also ongoing studies to determine the potential for molecular assays that use the swallowable devices to be used for surveillance of HGD and early EAC.

Sanghi and Thota (2019) presented various novel techniques for screening of BE such as unsedated trans-nasal endoscopy, Cytosponge with trefoil factor-3, balloon cytology, esophageal capsule endoscopy, liquid biopsy, electronic nose, and oral microbiome. These investigators noted that a qualitative study showed high acceptability and comfort level in patients undergoing Cytosponge procedure; VAS determined favorable acceptability (p < 0.001) in 93.9 to 99% patients. Brief episodes of sore throat and site abrasion with oozing blood was noted in 16.7% of patients, which resolved without any intervention. The authors concluded that Cytosponge with TFF3 appeared promising over endoscopy and can be utilized in the primary care clinic if applicable to the general population. They stated that Cytosponge and Esocheck non-endoscopic balloon are being validated in larger studies before they can be implemented for clinical use.

Esophageal Microbiota for Detection of Barrett's Esophagus

Lv and colleagues (2019) stated that the incidence of EAC has increased in recent decades, and its 5-year survival rate is less than 20%. As a well-established precursor, patients with BE have a persistent risk of progression to EAC. Many researchers have already identified some factors that may contribute to the development of BE and EAC, and the identified risks include GER, male sex, older age, central obesity, tobacco smoking, Helicobacter pylori (H. pylori) eradication, and the administration of PPIs and antibiotics. The human gut harbors trillions of microorganisms, the majority of which are bacteria. These microorganisms benefit the human host in many ways, such as helping in digestion, assisting in the synthesis of certain vitamins, promoting the development of the GI immune system, regulating metabolism and preventing invasion by specific pathogens. In contrast, microbial dysbiosis may play important roles in various diseases, such as inflammation and cancers. The composition of the microbiota located in the normal esophagus is relatively conserved without distinct microbial preferences in the upper, middle and lower esophagus. Six major phyla constitute the esophageal microbiota,
including Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Fusobacteria and TM7, similar to the oral microbiota. Streptococcus dominates the esophageal microbiota. However, the microbiota varies in different esophageal diseases compared to that in the healthy esophagus. The type I microbiota, which is primarily composed of gram-positive bacteria, is closely associated with the normal esophagus, while type II microbiota has enriched gram-negative bacteria and is mainly associated with the abnormal esophagus. These increased gram-negative anaerobes/microaerophiles include Veillonella, Prevotella, Haemophilus, Neisseria, Granulicatella and Fusobacterium, many of which are associated with BE. The microbial diversity in the esophagus is decreased in EAC patients, and Lactobacillus fermentum is enriched compared to that in controls and BE patients. Furthermore, the microbiota may be associated with BE and EAC by interacting with their risk factors, including central obesity, GER, H. pylori, administration of PPIs and antibiotics. Thuse, a large gap in research must be bridged to elucidate the associations among these factors. Some studies have already proposed several potential mechanisms by which the microbiota participates in human carcinogenesis by complicated interactions with the human host immune system and signaling pathways. The activation of the LPS-TLR4-NF-κB pathway may contribute to inflammation and malignant transformation. The authors concluded that this exciting field of GI microbiota allows researchers to unravel the mystery of carcinogenesis from another perspective. They stated that further prospective studies with sophisticated techniques are needed to examine if the microbiota changes before or after disease onset, to improve the understanding of the pathogenesis, and to find novel targets for prevention, diagnosis and therapy, which could offer more cost-effective and relatively safe choices.

Mitochondrial DNA Deletions for Detection of Barrett’s Esophagus

Keles and colleagues (2019) stated that esophageal cancer is the 8th most common cancer globally. Esophageal adenocarcinoma (EA) and esophageal squamous-cell carcinoma (ESCC) are the 2 major types of esophageal cancer with poor prognosis. The mechanisms of the progression of normal esophagus to BE and EA are not fully understood. Mitochondria play a central role in generating energy, apoptosis and cell proliferation. Mutations of mitochondrial DNA (mtDNA) have been identified in many diseases including cancers. Mutations of mtDNA were examined as a part of carcinogenesis. These researchers examined if the 5 kb and 7.4 kb mtDNA deletions are important in the progression of normal esophagus to BE and EA. In this study, the frequency of the 5 kb and 7.4 kb deletions in mtDNA were studied in specimens ranging from normal esophageal tissue to BE and EA and also from ESCC; 76 paraffin-embedded tissue samples were studied; and 4 couple primers were used. The negative control and the positive control PCR product were detected in all analyzed samples. The fusion PCR products, which represent the presence of the deletions, were not detected in any of the
samples. The authors concluded that these mtDNA deletions were not associated with progression of normal esophagus to BE and EA and they do not have an important role in detecting esophagitis, BE, EA, and ESSC.

Volumetric Laser Endomicroscopy for Evaluation of Barrett’s Esophagus

Trindade and associates (2017) noted that the incidence of EAC is on the rise despite widespread appreciation that the precursor lesion is BE. Studies have shown that some patients known to have BE develop cancer despite their enrollment in conventional endoscopic surveillance programs. This highlighted the need for advanced endoscopic imaging to help identify early neoplasia and prevent its progression to esophageal cancer. Recently, a wide-field, 2nd-generation OCT endoscopic platform called volumetric laser endomicroscopy (VLE) was cleared by the FDA and made commercially available for advanced imaging in BE. These investigators discussed current literature on VLE imaging in BE. Based on ex-vivo studies, criteria have been established for identifying BE-associated neoplasia. In addition, recent studies, case series, and case reports have demonstrated that VLE is well-tolerated, effective, and can target neoplasia. The authors concluded that VLE is a new advanced imaging platform for BE with considerable promise to target BE-associated neoplasia. The following are needed to establish VLE’s clinical role: studies showing incremental yield of dysplasia detection using VLE, studies to determine VLE’s in-vivo diagnostic accuracy for identifying and classifying BE-associated neoplasia, and studies on the cost-efficacy of VLE.

Aziz and Fatima (2018) stated that EAC is one of the deadliest carcinoma faced by gastroenterologists. Any insult to esophagus that causes replacement of normal squamous epithelium with columnar intestinal epithelium is labelled as the initiating event of the metaplasia-neoplasia sequence. Currently, endoscopically obtained biopsies are used to detect neoplastic changes in patients with BE; however, it is not cost-effective and hence a better screening modality is needed. The authors stated that VLE has been under study for the past few years and has shown promising results to overcome the shortcoming faced in the biopsy samplings. It is a 2nd-generation OCT that provides high-resolution cross-sectional imaging of the esophageal mucosa using near-infrared light.

Smith and colleagues (2019) noted that VLE uses OCT for real-time, microscopic cross-sectional imaging. A US-based multi-center registry was constructed to prospectively collect data on patients undergoing upper endoscopy during which a VLE scan was performed. The objective of this registry was to determine usage patterns of VLE in clinical practice and to estimate quantitative and qualitative performance metrics as they are applied to BE management. All procedures utilized the NvisionVLE Imaging System (NinePoint Medical, Bedford, MA) which was used by investigators to identify the tissue types present, along with focal areas of concern.
Following the VLE procedure, investigators were asked to answer 6 key questions regarding how VLE impacted each case. Statistical analyses including neoplasia diagnostic yield improvement using VLE was performed. A total of 1,000 patients were enrolled across 18 U.S. trial sites from August 2014 through April 2016. In patients with previously diagnosed or suspected BE (894/1,000), investigators used VLE and identified areas of concern not observed on WLE in 59 % of the procedures; VLE imaging also guided tissue acquisition and treatment in 71 % and 54 % of procedures, respectively; VLE as an adjunct modality improved the neoplasia diagnostic yield by 55 % beyond the standard of care practice. In patients with no prior history of therapy, and without visual findings from other technologies, VLE-guided tissue acquisition increased neoplasia detection over random biopsies by 700 %. Registry investigators reported that VLE improved the BE management process when used as an adjunct tissue acquisition and treatment guidance tool. The authors concluded that this registry-based study demonstrated the potential for VLE to fill clinically relevant gaps in the ability to evaluate and manage BE.

The authors stated that the utility of this analysis is subject to several limitations. As a post-market registry study, there was no defined protocol for imaging, image interpretation and tissue acquisition, and there was no control group for matched population comparisons. The early experience of users on VLE image interpretation may have resulted in over-calling areas of concern. Abnormalities located deeper in the esophageal wall could be targeted with forceps biopsies at one site, while other sites would utilize endoscopic resection techniques that are more likely to remove the target. All of these discrepancies could affect any calculations regarding the adjunctive yield of VLE-targeted sampling. Further analysis of the global detection rate of dysplasia by site did not reveal any statistical difference. At the time of this study, image interpretation was performed using previously published guidelines for detection of neoplasia in BE with OCT. Challenges with histopathological diagnosis of LGD limited the development of VLE criteria for LGD. As such, the analyses in this study focused on neoplasia. Current guidelines suggest that treatment of LGD is acceptable so detection of LGD with VLE should be addressed in a future study. Additionally, the characteristic image features that maximized sensitivity and specificity of confirmatory biopsies must be optimized. Recently, Leggett et al (2016) established an updated step-wise diagnostic algorithm to detect dysplasia based on similar VLE features used in this study. This diagnostic algorithm achieved 86 % sensitivity, 88 % specificity, and 87 % diagnostic accuracy to detect BE dysplasia with almost perfect interobserver agreement among 3 raters (kappa = 0.86). Further optimization of VLE image features for identifying dysplasia and neoplasia are ongoing. Other limitations of the study included the lack of central pathology for interpretation of specimens, which could affect (positively or negatively) the reported benefit of VLE in finding dysplasia. However, this study focused on neoplasia where there is less inter-observer variability compared to LGD. Finally, as a non-randomized study conducted mostly at large BE referral centers with possibly higher pre-test probability of neoplasia, it was plausible that their validity in a community setting is limited.
However, the large sample size, its heterogeneity, plus variation in technique by site likely restored at least some of the external validity of the findings.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>43100</td>
<td>Excision of lesion, esophagus, with primary repair; cervical approach</td>
</tr>
<tr>
<td>43101</td>
<td>thoracic or abdominal approach</td>
</tr>
<tr>
<td>43107</td>
<td>Total or near esophagectomy, without thoracotomy; with pharyngogastrostomy or cervical esophagogastrostomy, with or without pyloroplasty (transhiatal)</td>
</tr>
<tr>
<td>43108</td>
<td>with colon interposition or small intestine reconstruction, including intestine mobilization, preparation, and anastamosis(es)</td>
</tr>
<tr>
<td>43112</td>
<td>Total or near esophagectomy, with thoracotomy; with pharyngogastrostomy or cervical esophagogastrostomy, with or without pyloroplasty</td>
</tr>
<tr>
<td>43113</td>
<td>with colon interposition or small intestine reconstruction, including intestine mobilization, preparation, and anastamosis(es)</td>
</tr>
<tr>
<td>43116</td>
<td>Partial esophagectomy, cervical, with free intestinal graft, including microvascular anastamosis, obtaining the graft and intestinal reconstruction</td>
</tr>
<tr>
<td>43117</td>
<td>Partial esophagectomy, distal two-thirds, with thoracotomy and separate abdominal incision, with or without proximal gastrectomy; with thoracic esophagogastrostomy, with or without pyloroplasty (Ivor Lewis)</td>
</tr>
<tr>
<td>43118</td>
<td>with colon interposition or small intestine reconstruction, including intestine mobilization, preparation, and anastamosis(es)</td>
</tr>
<tr>
<td>43121</td>
<td>Partial esophagectomy, distal two-thirds, with thoracotomy only, with or without proximal gastrectomy, with thoracic esophagogastrostomy, with or without pyloroplasty</td>
</tr>
<tr>
<td>43122</td>
<td>Partial esophagectomy, thoracoabdominal or abdominal approach, with or without proximal gastrectomy; with esophagogastrostomy, with or without pyloroplasty</td>
</tr>
<tr>
<td>43123</td>
<td>with colon interposition or small intestine reconstruction, including intestine mobilization, preparation, and anastamosis(es)</td>
</tr>
<tr>
<td>43124</td>
<td>Total or partial esophagectomy, without reconstruction (any approach), with cervical esophagostomy</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
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<tr>
<td>43211</td>
<td>Esophagoscopy, flexible, transoral; with endoscopic mucosal resection</td>
</tr>
<tr>
<td>43217</td>
<td>Esophagoscopy, rigid or flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique</td>
</tr>
<tr>
<td>43229</td>
<td>Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed) [radiofrequency ablation]</td>
</tr>
<tr>
<td>43254</td>
<td>Esophagastroduodenoscopy, flexible, transoral; with endoscopic mucosal resection</td>
</tr>
<tr>
<td>43270</td>
<td>Esophagastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed) [radiofrequency ablation]</td>
</tr>
<tr>
<td>43279</td>
<td>Laparoscopy, surgical, esophagomyotomy (Heller type), with fundoplasty, when performed</td>
</tr>
<tr>
<td>43280</td>
<td>Laparoscopy, surgical, esophagogastric fundoplasty (eg, Nissen, Toupet procedures)</td>
</tr>
<tr>
<td>43286</td>
<td>Esophagectomy, total or near total, with laparoscopic mobilization of the abdominal and mediastinal esophagus and proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with open cervical pharyngogastrostomy or esophagogastrostomy (ie, laparoscopic transthiatal esophagectomy)</td>
</tr>
<tr>
<td>43287</td>
<td>Esophagectomy, distal two-thirds, with laparoscopic mobilization of the abdominal and lower mediastinal esophagus and proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with separate thoracoscopic mobilization of the middle and upper mediastinal esophagus and thoracic esophagogastrostomy (ie, laparoscopic thoracoscopic esophagectomy, Ivor Lewis esophagectomy)</td>
</tr>
<tr>
<td>43288</td>
<td>Esophagectomy, total or near total, with thoracoscopic mobilization of the upper, middle, and lower mediastinal esophagus, with separate laparoscopic proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with open cervical pharyngogastrostomy or esophagogastrostomy (ie, thoracoscopic, laparoscopic and cervical incision esophagectomy, McKeown esophagectomy, tri-incisional esophagectomy)</td>
</tr>
<tr>
<td>43325</td>
<td>Esophagogastric fundoplasty; with fundic patch (Thal-Nissen procedure)</td>
</tr>
<tr>
<td>43327</td>
<td>Esophagogastric fundoplasty partial or complete; laparotomy</td>
</tr>
<tr>
<td>43328</td>
<td>thoracotomy</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<td>----------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>+43338</td>
<td>Esophageal lengthening procedure (eg collis gastroplasty or wedge gastroplasty)</td>
</tr>
<tr>
<td></td>
<td>(list separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>+ 96570</td>
<td>Photodynamic therapy by endoscopic application of light to ablate abnormal tissue</td>
</tr>
<tr>
<td></td>
<td>via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)</td>
</tr>
<tr>
<td>+ 96571</td>
<td>each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

- Optical coherence tomography, Evaluation of esophageal microbiota and mitochondrial DNA deletions - no specific code:
  - 43206 Esophagoscopy, flexible, transoral; with optical endomicroscopy
  - 43252 Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
  - 43620 Gastrectomy, total; with esophagoenterostomy
  - 43621 Gastrectomy, total; with Roux-en-Y reconstruction
  - 43622 Gastrectomy, total; with formation of intestinal pouch, any type
  - 43631 Gastrectomy, partial, distal; with gastroduodenostomy
  - 43632 Gastrectomy, partial, distal; with gastrojejunoanastomosis
  - 43633 Gastrectomy, partial, distal; with Roux-en-Y reconstruction
  - 43634 Gastrectomy, partial, distal; with formation of intestinal pouch
  - 43644 Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
  - 43645 Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
  - 43770 - 43775 Bariatric Surgery - Laparoscopy
  - 43842 - 43848 Gastric restrictive procedure, gastric bypass
  - 43842 - 43848 Gastric restrictive procedure, open port component only
  - 88364 In situ hybridization (eg, FISH), per specimen; each additional single probe stain procedure (List separately in addition to code for primary procedure)
  - 88365 In situ hybridization (eg, FISH), per specimen; initial single probe stain procedure
  - 88366 In situ hybridization (eg, FISH), per specimen; each multiplex probe stain procedure
  - 91110 Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), esophagus through ileum, with physician interpretation and report
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>91111</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), esophagus</td>
</tr>
<tr>
<td></td>
<td>with physician interpretation and report</td>
</tr>
<tr>
<td>J9600</td>
<td>Injection, porfimer sodium, 75 mg</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

Q0083 - Q0085 Chemotherapy administration

ICD-10 codes covered if selection criteria are met:

K22.70 - K22.719 Barrett's esophagus

Endoscopic Submucosal Dissection:

No specific code

Other CPT codes related to the CPB:

43200 - 43273 Endoscopy [not covered for endoscopic submucosal dissection for Barrett's esophagus and esophageal cancer]

The above policy is based on the following references:

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112. Bergman JJ. Barrett’s esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2015.


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0728
Barrett's Esophagus

There are no amendments for Medicaid.