The American Society for Gastrointestinal Endoscopy PIVI on
Imaging in Barrett's Esophagus
(Long form)

The PIVI Initiative

The PIVI initiative is an ASGE program that aims to identify important clinical questions related to endoscopy and to establish a priori diagnostic and/or therapeutic thresholds for endoscopic technologies designed to resolve these clinical questions. Additionally, PIVIs may also outline the data and or the research study design required for proving an established threshold is met. Once endoscopic technologies meet an established PIVI threshold, those technologies are appropriate to incorporate into clinical practice presuming the appropriate training in that endoscopic technology has been achieved. The ASGE encourages and supports the appropriate use of technologies that meet its established PIVI thresholds.

The PIVI initiative was developed primarily to direct endoscopic technology development toward resolving important clinical issues in endoscopy. The PIVI initiative is also designed to minimize the possibility that potentially valuable innovations are prematurely abandoned due to lack of utilization and to avoid widespread use of an endoscopic technology before clinical studies documenting their effectiveness have been performed. The following document, or PIVI, is one of a series of statements defining the diagnostic or therapeutic threshold that must be met for a technique or device to become considered appropriate for incorporation into clinical practice. It is also meant to serve as a guide for researchers or those seeking to develop technologies that are designed to improve digestive health outcomes.

An ad hoc committee under the auspices of the existing ASGE Technology and Standards of Practice Committees Chairs develops PIVIs. An expert in the subject area chairs the PIVI committee, with additional committee members chosen for their individual expertise. In preparing this document, evidence-based methodology was employed, using a MEDLINE and PubMed literature search to identify pertinent clinical studies on the topic. PIVIs are ultimately submitted to the ASGE Governing Board for approval, as is done for all Technology and Standards of Practice documents. This document is provided solely for educational and informational purposes and to support incorporating these endoscopic technologies into clinical practice. It should not be construed as establishing a legal standard of care.

Imaging in Barrett's Esophagus PIVI
(Long form)

I. General clinical area of this PIVI:

Real time imaging of Barrett's esophagus.

II. Background and statement of clinical relevance

The clinical problem addressed by the PIVI is the effectiveness, cost, and compliance of current surveillance protocols. Endoscopic surveillance of Barrett's esophagus (BE), as currently practiced, has numerous shortcomings. Dysplasia and early adenocarcinoma may be endoscopically indistinguishable from non-dysplastic tissue. The distribution of dysplasia and cancer is highly variable, and even the most thorough biopsy surveillance program has the potential for sampling error. Current surveillance programs are expensive and time consuming. Survey data indicate that while surveillance is widely practiced, there is marked variability in the technique and interval of surveillance as practice guidelines are not widely followed.[1-4] Recent work by Abrams et al found that adherence to guidelines (obtaining 4 quadrant biopsies every 2 cm) was seen in only 51% of cases and furthermore, the longer the length of the Barrett's segment, the worse the adherence.[4]

III. Specific clinical issues addressed by this PIVI

What performance characteristics are required for an imaging technology to eliminate the need for random biopsies during endoscopic surveillance of patients with non-dysplastic Barrett's?

IV. Thresholds recommended for this PIVI

To eliminate the need for random mucosal biopsies during the endoscopic surveillance of patients with non-dysplastic Barrett's esophagus, an imaging technology with targeted biopsies should have a per patient sensitivity of ≥90% and a negative predictive value (NPV) ≥98% for detecting high grade dysplasia (HGD) or early esophageal adenocarcinoma (EAC), compared to the current standard protocol (white light endoscopy and targeted and random 4 quadrant biopsies every 2 cm). In addition, the new imaging technology should have a specificity that is

sufficiently high (80%) to allow a reduction in the number of biopsies (compared with random biopsies).

V. Summary explanation of thresholds recommended for this PIVI

The majority of the Barrett's patients encountered in clinical practice are those with non-dysplastic Barrett's esophagus. These patients have a very low incidence of HGD and EAC development; therefore, the vast majority of patients undergoing surveillance have multiple biopsies obtained that show no evidence of HGD/EAC. The important clinical question is whether the use of endoscopic imaging based surveillance can permit fewer biopsies and more efficient and cost-effective surveillance?

For populations with a low prevalence of disease, the most important metrics for a diagnostic test are the sensitivity and the NPV. The current standard endoscopic approach to detect dysplasia in Barrett's detection is random 4 quadrant biopsies every 2 cm, along with targeted biopsies of suspicious lesions using white light endoscopy. Prior clinical trials have reported that this biopsy protocol has a sensitivity ranging from 28-85% for the detection of patients with HGD/EAC. Analyses that have demonstrated the cost-effectiveness of BE surveillance have assumed that surveillance programs in BE patients would have a sensitivity of 85-90%. Therefore, for endoscopic imaging based surveillance to replace the current biopsy protocol, it should have a sensitivity of $\geq$90%.

The second issue to consider for any new diagnostic test is the specificity; new diagnostic tests should have a substantially higher specificity than random biopsies, but the exact value required for the new modality to be cost-effective depends upon the cost of the test. Since abnormal imaging requires biopsies for confirmation, new imaging methods should not result in more biopsies being obtained than would a random biopsy protocol. Although new methods likely require a higher specificity than random biopsies, a low cost endoscopic imaging technology could still be cost-effective through reductions in pathology costs with a relatively moderate specificity (moderate false positive rate) whereas a more expensive endoscopic imaging technology would need a higher specificity (low false positive rate) to be cost-effective. Based on the published literature, the specificity of biopsy protocols in patients with Barrett's

esophagus has ranged from 56-100%; therefore, we propose that any new technology should have a specificity that is at least 80%.

The goal of this PIVI is to propose performance targets for new imaging technologies that can ultimately lead to a reduction in the proportion of patients being biopsied for non-dysplastic Barrett's esophagus

VI. Methodology used for this PIVI

a. Focused clinical question used for directed literature review and analysis. A comprehensive data search was performed to answer focused clinical questions using a National Library of Medicine PubMed search engine.
b. Expert consensus.

Focused clinical questions were:

a. What is the risk of HGD or EAC in patients with non-dysplastic Barrett's?
b. What is the accuracy of current surveillance protocols (standard endoscopy) for detecting HGD/EAC?
c. What are operating characteristics of various imaging modalities for the diagnosis of HGD/EAC, ie, chromoendoscopy, narrow band imaging, confocal microscopy?
d. What are the costs associated with surveillance of Barrett's patients?

VII. Literature review results/summary

1. What is the risk of HGD or EAC developing during surveillance of non-dysplastic Barrett's?

Despite the alarming increase in the incidence of EAC, the precise incidence of cancer in patients with Barrett's esophagus is uncertain, with rates varying from approximately 1/52 to 1/694 years of follow up.[5] However, the cancer risk for a given patient with non-dysplastic Barrett's esophagus is quite low. The most recent meta-analysis of cancer risk in BE patients produced a pooled estimate of 0.6% per year.[6] The rate of progression to the combined end point of HGD or EAC was 1% per year. More importantly, this study again confirmed that EAC was an uncommon cause of death in Barrett's patients: only 7% of deaths were due to EAC whereas 93% of the deaths were due to other causes, the most common being cardiovascular disease, which accounted for 35% of the deaths. The most recent publication

to address this by Wani et al[7] found that the risk of progression to cancer was even lower than that described above. In a multicenter cohort study of 1204 patients, the incidence of cancer was 0.27% per year and the incidence of the combined endpoint of cancer and high-grade dysplasia was 0.63% per year. Furthermore, at 5 and 10 years of follow up, 98.6% and 97.1% of patients were cancer free, emphasizing the low incidence of HGD/EAC in non-dysplastic Barrett's patients.

2. What is the accuracy of current surveillance protocols (standard endoscopy) for detecting HGD/EAC?

A number of studies have evaluated the accuracy of current surveillance biopsy protocols (4 quadrant biopsies every 2cm and target biopsies for suspicious lesions) for the detection of HGD/EAC. This has usually been performed in the context of comparing the current standard with a new imaging technique. In a study by Canto et al,[8] 43 Barrett's patients were randomized to either white light endoscopy with random biopsies or methylene blue chromoendoscopy in a cross-over trial. The overall sensitivity for the detection of patients with HGD or EAC was 28% for white light endoscopy. Similar results were achieved by 2 additional studies comparing white light endoscopy with chromoendoscopy.[9, 10] Kara et al evaluated 47 patients with Barrett's esophagus[11, 12] and found that the sensitivity of white light endoscopy (target plus random biopsies) for detecting HGD/EAC was 85%. Similarly, the overall specificity of biopsy protocols for the detection of HGD/EAC has ranged from 56-100%.

3. What are operating characteristics of various imaging modalities for the diagnosis of HGD/EAC, ie, chromoendoscopy, narrow band imaging, confocal microscopy?

In order to address this question, a comprehensive data search using a National Library of Medicine PubMed search engine was performed on March 10, 2011. Search terms included Barrett's esophagus crossed with any of the following terms: confocal endomicroscopy, narrow band imaging, methylene blue, indigo Carmine, acetic acid, chromoendoscopy, and virtual chromoendoscopy. The search was restricted to studies in English language journals. Only studies that reported the prevalence and per lesion or per patient sensitivity and specificity were included in the analysis. A total of 32 studies which included 3424 patients with Barrett's esophagus were identified and are shown in Table 1. 15 studies which included

1620 patients had data sufficient to calculate a per patient NPV. The vast majority of studies included patients with a high prevalence of neoplasia.

The primary outcome variable was per patient NPV for the detection of HGD/EAC based on targeted biopsies alone. If the NPV was not reported within the study, it was calculated based on the disease prevalence, per patient sensitivity, and per patient specificity, using standardized formulas. Overall the NPV for current advanced imaging methods ranged from 79-100%, with a mean NPV of 97%. The per patient sensitivity and specificity of new imaging techniques have ranged from 33-100% and 56-100% respectively (listed in Table 1).

Table 1: Review of studies evaluating performance characteristics of various imaging modalities.
(See table 1 at the end of the document.)

4. What are costs associated with surveillance of non-dysplastic Barrett's?

The primary costs associated with surveillance include physician time, nursing time, facility utilization (procedure rooms, time and equipment for patient scheduling, reminders, and patient preparation), sedation expenses, equipment outlays (endoscopes, biopsy forceps, imaging devices), pathology processing, pathologist charges, time lost from work for the patient, and time lost from work for persons accompanying the patient. Adoption of imaging could conceivably impact all of these except the last two (time lost from work).

The costs of procedures are difficult to estimate due to the proprietary nature of private insurance company data and differences in federal reimbursement based on geographic location. Table 2 shows costs based on Medicare reimbursement estimates for 2011 for endoscopy [13] and pathology [14] payments. Actual costs would depend upon surveillance frequency, geographic location, type of facility where the procedure was performed (ambulatory surgery unit vs hospital vs office), and the number of biopsy containers.

Table 2. Costs based on Medicare reimbursement estimates for 2011 for endoscopy [13] and pathology [14] payments.

Procedure	Facility Fee (pathology technical fee)*		Professional Fee*		Total Cost for ASC
	Ambulatory Surgery Center	Outpatient Hospital	Hospital or Ambulatory Surgery Center	In Office	
EGD with biopsy[1]	$344.10	$611.73	$174.64	$345.20	$518.74
Pathology per slide (CPT 88305)[2]	$68.99 (per block)		$105.03 (per slide)		$174.02

ASC: Ambulatory Surgery Center; * Sage rates are based on CMS rates and subject to adjustment whenever CMS does the same.[14]

1. Medicare National Average
2. Minnesota screening program reimbursement rates

Note: Actual costs would depend upon surveillance frequency, geographic location, type of facility where the procedure was performed (ambulatory surgery unit vs hospital vs office), and the number of biopsy containers.

VIII. Areas for Research

There are a number of research areas relevant to this PIVI. Having a better estimate of which patients are at greatest risk for developing esophageal cancer is important, as screening and surveillance efforts should be focused more on these patients, with perhaps less frequent or no surveillance in those patients at extremely low risk for developing cancer. New imaging techniques would need to be compared to the "current standard" available endoscope, which could change in the future as the next generation scopes will continue to have improved imaging. Future studies will need to compare the new imaging technology with the standard 4-quadrant biopsy protocol in the same patient population in order to determine whether the PIVI thresholds are met. Additionally, cost-effectiveness studies will need to be performed related to the operating characteristics of any new imaging modality compared to standard biopsy protocol in the same population.

Studies determining the operating characteristics for endoscopists at different levels of training including describing the learning curve, intra and inter observer variation, and level of confidence need to be carefully performed. In addition, demonstrating that endoscopists

can be trained to identify various patterns seen by the imaging modalities, and predict histology will be important. Finally, it will be essential to determine and compare the outcomes of new imaging techniques, total costs of current biopsy practices, avoiding biopsy of non-dysplastic Barrett's patients and targeting biopsy only to high yield areas.

IX. Training issues/establishment of competency

Training needs to be available to ensure the effectiveness of any new technology as it becomes widely available in non-research settings. Training might be in the context of learning a variety of contrast-enhanced endoscopic techniques such as high resolution endoscopy with magnification, dye-based image-enhanced endoscopy, and optical electronic enhanced endoscopy, or might just focus on a single enhanced imaging technique. Various methods of training would likely be used, including video and written training materials, hands-on courses using inanimate models, observational experiences with mentors, and hands-on training in patients with a mentor. Given that much of the training involves image pattern recognition, it is likely that aspects of the training could easily be performed through internet based learning options. Studies would be needed to determine an optimal number of training cases (either real-time or from an image/video library) needed before achieving the expected performance competence as described in the PIVI.

Quality measures would also need to be developed to ensure consistent, high confidence examinations. This might involve correlating the endoscopist's histologic prediction based on enhanced endoscopic images with the actual pathologic histology, although this can be time consuming and require a large number of patients. Another quality measure might be having an endoscopist review a series of endoscopic still images and videos, and then test the learner on their image interpretation compared to either a pathologic gold standard or an expert consensus panel. This could be used both as an assessment and teaching tool. It could also be used to test for intra and inter observer agreement.

Gastroenterologic societies, such as the American Society for Gastrointestinal Endoscopy (ASGE), would need to develop position statements on minimum requirements for both trainees and practicing clinicians to start using enhanced imaging techniques instead of pathologic biopsies for evaluation of Barrett's esophagus.

X. Factors considered by the PIVI committee in establishing the thresholds

1. Limitations of current methods for surveillance of patients with Barrett's esophagus.
2. Low risk of HGD/EAC in patients with non-dysplastic Barrett's esophagus.
3. Costs of standard endoscopy and biopsy.

XI. Other issues addressed by the PIVI committee:

The widespread use of a new technology in patients with Barrett's esophagus would be influenced by cost-effectiveness, training and quality standards, reimbursement, and patient selection (Table 3). Cost-effectiveness would depend on whether the additional costs of using a new technology were offset by reduced pathology costs, improved endoscopy unit efficiency, or significantly increased diagnostic accuracy. The utilization of new technologies by large numbers of practitioners would require training and performance quality measures to ensure consistent, high confidence examinations. Reimbursement might need to be adjusted if more expensive equipment or longer procedure times were necessary. Patient selection for a new imaging modality might need to be individualized depending on whether a Barrett's patient was low risk or at higher risk for development of esophageal cancer (ie, diagnosis of Barrett's at a young patient age, family history of Barrett's or esophageal cancer, long segment Barrett's, personal history of dysplasia/cancer, and/or history of ablation).

*Table 3. Factors that can potentially influence costs of surveillance endoscopy in patients with Barrett's esophagus from published studies: standard endoscopy and new imaging **

Factors Potentially Influcencing Costs	Study Author	Population	Imaging Technique	Standard Endoscopy	Imaging-Based Endoscopy	Net Effect on Costs for Imaging Modality
Average Procedure time (minutes)	Curvers et al[15]	Known low grade dysplasia	Multi-modality	12:22 mins (SD 3:24)	19:41 mins (SD 7:24)	Increased
Number of visible suspicious lesions requiring biopsies	Curvers et al[15]	Known low grade dysplasia	Multi-modality	82	156 (96 assigned as suspicious by NBI)	Increased numbers of suspicious areas requiring biopsy
Total number of biopsies obtained	Wolfsen et al[16]	Previously detected dysplasia	Narrow Band	8.5 mean per patient	4.7 mean per patient	Decrease in total number of biopsies
	Sharma et al[17]	Patients presenting for surveillance	Confocal endo-microscopy of areas detected by standard or narrow band image	856 total in the sample	608* total in the sample	Decrease in total number of biopsies

*approximate (calculated from data)

XII. PIVI committee:

Chairs: Prateek Sharma, MD, FASGE and Thomas J. Savides, MD, FASGE

Members: Marcia Irene I. Canto, MD, FASGE, Douglas Corley, MD, PhD, MPH, Gary W. Falk, MD, MS, FASGE, John Goldblum, MD, Kenneth K. Wang, MD, FASGE, Michael B. Wallace, MD, FASGE, Herbert C. Wolfsen, MD, FASGE.

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Table 1: Review of studies evaluating performance characteristics of various imaging modalities.

Study	References	Method	N	Study design	Endoscope	Prevalence neoplasia (%)	Per lesion Sensitivity	Per lesion Specificity	Per pt Sensitivity	Per pt Specificity	Per Pt PPV	Per pt NPV	Calculated per pt NPV
Kara et al[12]	Endoscopy 2005; 37:929-36.	NBI	28	RC	GIF 240z	50	-	-	79	-	-	93	-
Pohl et al[18]	Endoscopy 2007; 39:492-496	FICE	57	Study design	Fuji EG 590 ZW	42	87	-	92	-	-		-
Curvers et al[19]	Gut 2008;57:167-72	HRE-AFI-NBI	84	CS	GIF 240z	36	93	58	90	-	-	-	-
Kara et al[20]	GIE 2006; 64:176-85.	HRE-AFI	20	CS	GIF 240z	70	100	74	100	98	-	-	100

Kara et al[21]	GIE 2006;64:155-166	NBI	63	CS	GIF 240z	-	94	76	-	-	-	-	-
Bajbouj et al[22]	Endoscopy 2010;42:435-40	pCLE (s-probe)	68	CS	S probe	16	12	95	60	95	67	93	93
Wallace et al[23]	GIE 2010; 72:19-24.	pCLE	20	CS	UHD probe	55	88	96	88	96	91	88	87
Sharma et al[24]	GIE 2011 [in press]	pCLE	101	-	UHD probe	30	76	84	100	56	50	100	100
Kiesslich et al[25]	Clin Gastroenterol Hepatol 2006:4:979-87	eCLE	63	-	Pentax EC3870KCIL K)	24	93	98	-	-	-	-	-
Sharma et al[26]	GIE 2006:64:167-175	NBI	51	CS	GIF 240z	-	100	99	100	98	-	-	100

Singh et al[27]	Endo 2008:40:457-63	NBI	109	CS	GIF 240z	13	96	99	93	97	81	99	99
Goda et al[28]	GIE 2007:65:36-45	NBI	58	CS	GIF 240z	10	100	100	100	100	100	100	100
Anagnostopoulos et al[29]	APT 2007:26:501	NBI	50	CS	GIF 240z	-	90	100	83	98	-	-	100
Singh et al[30]	Scand J Gastro 2009:44:85-94	NBI	21	CS	GIF 240z	14	89	95	-	-	-	-	-
Curvers et al[31]	Gastro 2010;139:1106	HRE-AFI-NBI	87	CS	GIF 240z	63	-	-	65	-	-	-	-
Wolfsen et al[16]	Gastro 2008;135:24-31	NBI	65	CS	GIF H 180	32	-	-	100	-	-	100	-

Curvers et al[32]	Gastro 2008;134:670	NBI	14	CS	GIF 240z	-	-	-	-	-	-	-	-
Longcroft-Wheaton et al[33]	CGH 2010;8:843	AA	119	CS	Fuji 590zw	46	-	-	96	81	-	-	96
Vazquez-Iglesias et al[34]	Eur J Gastrohep;2007;19:187	AA	100	CS	NA	13	-	-	100	98	86	100	100
Hoffman et al[35]	GIE 2006;64:1-8	AA	31	CS	GIF 160z	6	-	-	100	-	-	-	-
Dunbar et al[36]	GIE 2009;70:645-54	eCLE	39	CS	Pentax EC3870KCIL K)	33	-	-	-	-	-	-	-
Canto et al[8]	GIE 2000;51:560-568	MB	43	CS	-	-	-	-	-	-	-	-	-

Wo et al[9]	GIE 2001;54:294-301	MB	35	CS	-	-	-	-	-	-	-	-	-
Ragunath et al[10]	Endoscopy 2003:35:998-1003	MB	57	CS	-	3	-	-	100	98	100	80	100
Saporiti et al[37]	Arq Gastroenterol 2003;40:139-47	MB	45	CS	-	0	-	-	-	-	-	-	-
Gossner et al[38]	Dig Liver Dis 2006;38:724-729	MB	86	CS	-	100	98	-	87	-	-	-	-
Lim et al[39]	GIE 2006;64:195-199	MB	30	CS	-	27	-	-	33	92	15	50	79
Horwhat et al[40]	Am J Gastro 2008;103:546-554	MB	48	CS	gif 140	44	67	79	76	-	-	-	-

Pohl et al[41]	Am J Gastro 2010; 105:2350–2356	AA	701	CS	Fuji EG 590 HR, or 450 WR	13	82	-	97	67	30	99	99
Sharma et al[42]	Endoscopy 2006;38:1206-1212	IC	56	CS	GIF 160z	11	-	-	67	100	100	96	96
Sharma et al[43]	Gut 2003:52:24-27	IC	80	CS	GIF 160z	8	100	100	100	100	100	100	100
Lim et al[39]	GIE 2006;64:195199	MB	30	CS	-	27	-	-	33	92	15	50	79
Horwhat et al[40]	Am J Gastro 2008;103:546-554	MB	48	CS	gif 140	44	67	79	76	NA	NA	NA	-
Pohl et al[41]	Am J Gastro 2010; 105:2350–2356	AA	701	CS	Fuji EG 590 HR, or 450 WR	13	82	-	97	67	30	99	99

Sharma et al[42]	Endoscopy 2006;38:1206-1212	IC	56	CS	GIF 160z	11	-	-	67	100	100	96	96
Sharma et al[43]	Gut 2003:52:24-27	IC	80	CS	GIF 160z	8	100	100	100	100	100	100	100
Yuki et al[44]	Dig Liver Dis 2006;38:296	CV	818	CS	GIFH260	2	96	67	-	-	-	-	-
Fortun et al[45]	APT 2006;23:735-742	AA	64	CS	GIF Q240Z	7	100	100	-	-	-	-	-

Abbreviations: CS-Cross Sectional Study, RCT-Randomized Cross over Trial, PPV-Positive Predictive value, NPV-Negative Predictive value, AA-acetic acid, NBI-narrow band imaging, FICE-fujinon intelligent chromoendoscopy, MB-methylene blue, CV-crystal violet, IC-indigo carmine, HRE-high resolution endoscopy, AFI-auto-fluorescence imaging, pCLE-probe based confocal laser endomicroscopy, eCLE-endoscope based confocal laser endomicroscopy