Clinical Policy Bulletin:  
In Vivo Analysis of Colorectal Polyps and Inflammatory Bowel Disease  
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Policy

Aetna considers in-vivo analysis of colorectal polyps (e.g., chromoendoscopy, confocal laser [fluorescent] endomicroscopy [including Cellvizio probe-based confocal laser endomicroscopy], endocytoscopy, EVIS EXERA 160A System, fiberoptic analysis, multi-band imaging, narrow-band imaging optical chromocolonoscopy, Optical Biopsy System, Pentax Confocal Laser System, and WavSTAT™ Optical Biopsy System) experimental and investigational because of insufficient evidence of its effectiveness.

Aetna considers confocal laser endomicroscopy (including Cellvizio probe-based confocal laser endomicroscopy) experimental and investigational for the diagnosis, prediction of disease course, and therapeutic responses of inflammatory bowel disease (Crohn's disease and ulcerative colitis).

Background

In the United States, colorectal cancer is the third most common cancer diagnosed among men and women and the second leading cause of death from cancer. Early stage colorectal cancers and pre-cancerous adenomatous lesions can be visualized and treated endoscopically. However, complications of colonoscopic polypectomy include hemorrhage (reported incidence of 0.2 % to 3 %) and perforation (reported incidence of 0.5 % to 3 %). In addition, biopsy and polypectomy are frequently performed for lesions that carry a low risk of malignancy in the colon. Thus, the ability to determine colorectal polyp pathology by endoscopy could potentially reduce the risks of polypectomy and improve the diagnosis of early colonic neoplasia.

A number of imaging technologies are under development that have the potential to enhance detection of colorectal neoplasia. Recent technology has led to the development of colonoscopes that are specifically designed to further improve visualization, including wide angle of view and high resolution. Traditionally,
white light colonoscopy (WLC) is used whereby the light source provides red, green and blue wavelength light sequentially by a rotation filter. However, flat lesions are often difficult to identify with WL and diagnosis is usually dependent on random biopsies. Newer colonoscopes equipped with non-white light imaging capabilities have been designed to enhance image contrast and potentially improve the visualization of lesions. Some of these methods include fiberoptic analysis, narrow band imaging, and confocal fluorescent endomicroscopy.

The Optical Biopsy System (SpectraScience, Inc., Minneapolis, MN) includes a laser light, a long optical fiber that the light passes through and a computer that analyzes the light given off by suspicious lesions. It received premarket approval (PMA) through the U.S. Food and Drug Administration (FDA) as an adjunct to lower gastrointestinal endoscopy for the evaluation of polyps less than 1 cm in diameter that the physician has not already elected to remove. The device is only to be used in deciding whether such polyps should be removed (which includes submission for histological examination). The FDA approval was based on an unpublished prospective, non-randomized phase II study. According to the information submitted by the manufacturer to the FDA, patients (n = 101) who had at least one polyp identified from a prior endoscopic examination, underwent another standard colonoscopy using the Optical Biopsy System. When a polyp was identified, the physician documented whether they thought the polyp was adenomatous or hyperplastic based on the visual assessment and whether they would remove the polyp. The optical fiber was placed on a region of the polyp and the tissue’s autofluorescence was evaluated from three different locations on the polyp. The effectiveness of the Optical Biopsy System was characterized by its ability to correctly identify adenomatous polyps as adenomatous and to correctly identify hyperplastic polyps as hyperplastic either alone or in conjunction with the physician assessment. The sensitivity and specificity of the physician assessment alone were 82.7 % and 50 %, respectively, whereas, the combined sensitivity and specificity were 96.3 % and 33 %, respectively. The study demonstrated that the Optical Biopsy System, when used as an adjunctive tool, will increase the number of adenomatous polyps that are biopsied (i.e., increase the sensitivity of physician assessment), but will also increase the number of hyperplastic polyps that are biopsied (i.e., decrease the specificity of physician assessment). Optimal methodologies for the endoscopic detection of dysplastic colonic lesions have yet to be outlined; thus, it is not clear what additional benefits this device would have over simply increasing the number of polyps chosen for biopsy through visual inspection. In addition, it is not known whether the performance of the Optical Biopsy System would be different by physicians who are less experienced and skilled than those who participated in the phase II clinical study.

Pilot studies have demonstrated the safety and feasibility of polyp detection using narrow-band imaging (NBI) (Su et al, 2006; Rastogi et al, 2007; Tischendorf et al, 2007; East et al, 2008). Evaluating NBI studies, however, has been difficult because of the lack of standardization between NBI systems (Emura et al, 2008).

The Evis Exera Xenon Light Source CLV-160A (Olympus Medical Systems, Melville, NY) is a video processing system that received pre-marketing clearance from the FDA through the 510(k) process. It is intended for endoscopic diagnosis,
treatment and video observation and has an optional filter which allows the user to select either standard WL illumination or NBI.

Rogart et al (2008) compared WL with NBI for the differentiation of colorectal polyps in vivo during colonoscopy. Standard WL colonoscopy was performed with the Olympus 180-series colonoscopes. Each detected polyp was first characterized by WL and then by NBI. Modified Kudo pit pattern and vascular color intensity (VCI) were recorded, and the histology was predicted. Endoscopists were given feedback every 2 weeks. Main outcome measurements were overall accuracy and sensitivity and specificity of endoscopic diagnosis by using WL alone and with NBI, as well as improvement in endoscopists’ performance. A total of 265 polyps were found in 131 patients. Diagnostic accuracy was 80 % with NBI and 77 % with WL (p = 0.35). Narrow-band imaging performed better than WL in diagnosing adenomas (sensitivity 80 % versus 69 %, p < 0.05). Non-adenomatous polyps were more likely to have a light VCI compared with adenomas (71 % versus 29 %, p < 0.001). During the second half of the study, NBI accuracy improved, from 74 % to 87 %, and out-performed an unchanged WL accuracy of 79 % (p < 0.05). Overall, NBI was not more accurate than WL in differentiating colorectal polyps in vivo; however, once a learning curve was achieved, NBI performed significantly better. The authors concluded that further refinements of an NBI pit-pattern classification and VCI scale are needed before broad application to clinical decisions regarding the necessity of polypectomy can be made.

Rex (2009) evaluated the ability of the Olympus Exera 180 high-definition colonoscope (Olympus America, Inc., Center Valley, PA) with NBI to predict colorectal polyp histology. A library of 320 endoscopic photographs with correlated histologic information were used to identify endoscopic features associated with adenomatous and hyperplastic histology. These features were tested in a prospective study of 451 consecutively identified colorectal polyps. Polyps were observed endoscopically and assigned a designation of high or low confidence. The primary end points were the predictive value of high-confidence endoscopic interpretations of adenoma and hyperplastic histology for polyps greater than 5 mm in size. Endoscopic predictions of adenoma and hyperplastic histology were made with high confidence for 80 % and 83 % of cases, respectively. High-confidence predictions were more likely than low-confidence predictions to be correct (p < 0.001). High-confidence predictions of adenoma and hyperplastic histology were correct for 91 % and 95 %, respectively, of polyps greater than 5-mm in size. The author concluded that the introduction of confidence levels to the endoscopic interpretation of colorectal polyp histology allowed sufficient accuracy for the use of the Exera narrow-band imaging system in the identification of distal hyperplastic polyps that do not need resection, as well as to plan post-polypectomy surveillance without pathologic evaluation of polyps 5-mm in size or smaller.

In a prospective randomized study, Adler et al (2008) evaluated NBI versus conventional colonoscopy for adenoma detection. Eligible patients presenting for diagnostic colonoscopy were randomly assigned to undergo wide-angle colonoscopy using either conventional high-resolution imaging or NBI during instrument withdrawal. The primary outcome parameter was the difference in the adenoma detection rate between the 2 techniques. A total of 401 patients were
included (mean age of 59.4 years, 52.6 % men). Adenomas were detected more frequently in the NBI group (23 %) than in the control group (17 %), however, the difference was not statistically significant (p = 0.129). When the two techniques were compared in consecutive subgroups of 100 study patients, adenoma rates in the NBI group remained fairly stable, whereas these rates steadily increased in the control group (8 %, 15 %, 17 %, and 26.5 %, respectively). Significant differences in the first 100 cases (26.5 % versus 8 %; p = 0.02) could not be maintained in the last 100 cases (25.5 % versus 26.5 %, p = 0.91). The authors concluded that the increased adenoma detection rate of NBI colonoscopy were not statistically significant and whether the increasing adenoma rate in the conventional group was caused by a training effect of better polyp recognition on NBI remains speculative.

In a randomized controlled trial (RCT), Kaltenback et al (2008) compared NBI versus WLC. Patients were randomly assigned to undergo a colonoscopic examination using NBI or WLC. All patients underwent a second examination using WLC as the reference standard. The primary end point was the difference in the neoplasm miss rate, and secondary outcome was the neoplasm detection rate. Patients who underwent tandem colonoscopy (n = 276) experienced no significant difference of miss or detection rates between NBI or WLC. Of the 135 patients in the NBI group, 17 patients (12.6 %; 95 % confidence interval [CI]: 7.5 to 19.4 %) had a missed neoplasm, as compared with 17 of the 141 patients (12.1 %; 95 % CI: 7.2 to 18.6 %) in the WLC group with a miss rate risk difference of 0.5 % (95 % CI: -7.2 to 8.3); 130 patients (47 %) had at least 1 neoplasm. Missed lesions with NBI showed similar characteristics to those missed with WLC. All missed neoplasms were tubular adenomas, the majority (78 %) was less than or equal to 5.0 mm and none were larger than 1 cm (1-sided 95 % CI: up to 1%). Non-polyoid lesions represented 35 % (13/37) of missed neoplasms. The authors concluded that NBI did not improve the colorectal neoplasm miss rate compared to WLC and that the neoplasm detection rates were similar using NBI or WLC.

It is not known whether NBI improves patient outcomes. Studies that compared NBI to WLC reported similar neoplasm detection rates and there is a lack of standardization between NBI systems making it difficult to interpret the studies.

Confocal endomicroscopy is a new endoscopic technique that provides microscopic images of cellular morphology in the gastro-intestinal tract during ongoing endoscopy. The peer-reviewed literature for confocal endomicroscopy consists of small non-randomized safety and feasibility studies (Odagi et al, 2007; Hsiung et al, 2008; Watanable et al, 2008). This methodology represents a promising diagnostic imaging approach for the early detection of colorectal cancer, however, there is insufficient evidence of its effectiveness.

According to a review by Anandasabapathy (2008) on emerging optical techniques for the detection of colorectal neoplasia, autofluorescent imaging and NBI are "red flag" techniques which enhance visualization of mucosal change(s) and complementary technologies, such as confocal endomicroscopy and endocytoscopy provide subcellular imaging. However, it is unclear how these techniques impact clinical outcomes. Tissue biopsy is considered the gold
standard for histopathological diagnosis; furthermore, optimal methodologies for the endoscopic detection of dysplastic colonic lesions have yet to be outlined.

A systematic review by van den Broek et al (2009) found that narrow band imaging had high sensitivity and specificity for the differentiation of neoplastic from non-neoplastic colon polyps when used by experienced endoscopists, and that its accuracy was comparable to chromoendoscopy. A critique of this review by the Centre for Reviews and Dissemination (CRD, 2009) found, however, that this systematic review suffered from a number of limitations, which means that these findings should be interpreted with some caution. The systematic evidence review identified six studies (n = 1,222 patients) meeting including criteria that assessed the detection of neoplasia, including 4 RCTs and 2 tandem design studies (that compared the 2 techniques back to back). The CRD noted that one randomized study was not included in the meta-analysis. The CRD observed that eleven studies (n = 866 patients) on the differentiation of lesions were included in a table in the systematic evidence review but only 9 (n = 770) were included in the analysis and quality assessment table. One study assessed both and so contributed data to each analysis. The CRD noted that results of the quality assessment for the detection studies were not reported. The systematic evidence review found that studies on the differentiation of lesions all fulfilled items on use of an appropriate reference standard and avoidance of disease progression, partial verification, differential verification and incorporation bias. Items relating to test details, reference standard details, test bias and review bias were poorly reported. Only 4 studies included an appropriate patient spectrum and only 3 reported sufficient details of selection criteria. The systematic evidence review found that the proportion of patients with at least 1 adenoma detected by narrow-band imaging was similar to the proportion detected by white-light endoscopy (pooled odds ratio 1.19, 95 % CI: 0.86 to 1.64; 3 RCTs) as was the mean number of adenomas detected (relative ratio of means 1.23, 95 % CI: 0.93 to 1.61; 3 RCTs). In the 2 observational studies, the adenoma miss rates of white-light endoscopy were 40 % (29/72) and 46 % (21/46) for each study. Regarding the use of narrow band imaging in the differentiation of lesions, the review excluded 3 studies on the differentiation of lesions from the metaanalysis as they included highly selected patient groups and were therefore thought to be biased. Based on the remaining 6 studies, the pooled sensitivity of narrow-band imaging for the differentiation of neoplastic compared to non-neoplastic colon polyps was 92 % (95 % CI: 89 to 94) and pooled specificity was 86 % (95 % CI: 80 to 91). Five studies also reported on the accuracy of chromoendoscopy. Pooled sensitivity was reported to be 91% (95 % CI: 83 to 96) and pooled specificity was 89 % (95 % CI: 83 to 93). Four studies provided data on inter-observer agreement. Kappa values ranged from 0.48 to 1.0, suggesting moderate to excellent agreement. The authors of the systematic review concluded that narrow-band imaging showed high sensitivity and specificity for the differentiation of neoplastic from non-neoplastic colon polyps when used by experienced endoscopists, and that its accuracy was comparable to that of chromoendoscopy. In a critique of this systematic evidence review, the CRD (2009) found only limited study details reported, and that further details, especially in relation to the patients included in the studies, would have helped to assess the generalizability of findings. The CRD noted that not all studies reported to have fulfilled inclusion criteria and summarized in tables contributed to the analysis, and that the reasons for this are
unclear. The CRD also noted that heterogeneity was not formally assessed or 
investigated in this metaanalysis. The CRD stated that the conclusions of this 
meta analysis should be interpreted with some caution, due to the unclear 
generalizability of findings and the fact that some studies were excluded from the 
analysis without justification.

Benes and Antos (2009) examined the correlation between the results of an 
optical biopsy system and the histopathology report of the physical biopsy 
specimens of the same polyps removed at colonoscopy. Paired optical and 
physical biopsies were performed on 55 polyps with complete polypectomy of the 
same tissue. A total of 53 adenomatous polyps and 2 hyperplastic polyps were 
identified by the hospital pathologist. The optical biopsy system identified 52 
polyps as suspect (adenomatous) and 2 as non-suspect (hyperplastic). One 
villus adenoma could not be optically analyzed due to friability. The authors 
concluded that the WavSTAT Optical Biopsy System provides accurate 
information to the gastroenterologist to assist in distinguishing between 
hyperplastic and adenomatous polyps. However, the impact of this technology on 
health outcomes is unclear.

The American Society for Gastrointestinal Endoscopy (ASGE, 2008) published a 
technology status evaluation report regarding NBI. It stated that NBI may enhance 
the diagnosis and characterization of mucosal lesions in the gastrointestinal tract, 
especially as an adjunct to magnification endoscopy; however, standardization of 
image characterization, further image pathology correlation and validation, as well 
as the impact of these technologies on patient outcomes are needed before 
endorsing the use of NBI in the routine practice of gastrointestinal endoscopic 
procedures.

Kahi et al. (2010) noted that high-definition chromoscopy is used to increase the 
yield of colonoscopy for flat and depressed neoplasms; however, its role in 
average-risk patients undergoing routine screening remains uncertain. This study 
compared high-definition chromocolonoscopy with high-definition white light 
colonoscopy for average-risk colorectal cancer screening. Average-risk patients 
referred for screening colonoscopy at 4 United States medical centers were 
randomized to high-definition chromocolonoscopy or high-definition white light 
colonoscopy. The primary outcomes, patients with at least 1 adenoma and the 
number of adenomas per patient, were compared between the 2 groups. The 
secondary outcome was patients with flat or depressed neoplasms, as defined by 
the Paris classification. A total of 660 patients were randomized 
(chromocolonoscopy: 321, white light: 339). Overall, the mean number of 
adenomas per patient was 1.2 +/- 2.1, the mean number of flat polyps per patient 
was 1.4 +/- 1.9, and the mean number of flat adenomas per patient was 0.5 +/- 
1.0. The number of patients with at least 1 adenoma (55.5 % versus 48.4 %, 
absolute difference 7.1 %, 95 % CI: -0.5 % to 14.7 %), p = 0.07), and the number 
of adenomas per patient (1.3 +/- 2.4 versus 1.1 +/- 1.8, p = 0.07) were marginally 
higher in the chromocolonoscopy group. There were no significant differences in 
the number of advanced adenomas per patient (0.06 +/- 0.37 versus 0.04 +/- 
0.25, p = 0.3) and the number of advanced adenomas less than 10 mm per patient (0.02 
+/- 0.26 versus 0.01 +/- 0.14, p = 0.4). Two invasive cancers were found, 1 in 
each group; neither was a flat neoplasm. Chromocolonoscopy detected 
significantly more flat adenomas per patient (0.6 +/- 1.2 versus 0.4 +/- 0.9, p =

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0.01), adenomas less than 5 mm in diameter per patient (0.8 +/- 1.3 versus 0.7 +/- 1.1, p = 0.03), and non-neoplastic lesions per patient (1.8 +/- 2.3 versus 1.0 +/- 1.3, p < 0.0001). The authors concluded that high-definition chromocolonoscopy marginally increased overall adenoma detection, and yielded a modest increase in flat adenoma and small adenoma detection, compared with high-definition white light colonoscopy. The yield for advanced neoplasms was similar for the 2 methods. The authors concluded that these findings do not support the routine use of high-definition chromocolonoscopy for colorectal cancer screening in average-risk patients. The high adenoma detection rates observed in this study may be due to the high-definition technology used in both groups.

Neumann and colleagues (2011) noted that endocytoscopy (EC) enables in-vivo microscopic imaging at 1,400-fold magnification, thereby allowing the analysis of mucosal structures at the cellular level. In contrast to fluorescence imaging with confocal laser endomicroscopy (CLE), which allows analysis of mucosal structures up to 250 µm in depth, EC is based on the principle of contact light microscopy and only allows visualisation of the very superficial mucosal layer. These researchers systematically reviewed the feasibility and diagnostic yield of EC for in-vivo diagnosis of diseases. A systematic search of the literature on diagnostic interventions in the gastro-intestinal tract using EC was performed by searches in MEDLINE, Current Contents, PubMed, cross-references and references from relevant articles using the search terms "endocytoscopy", "endocytoscope", "magnification endoscopy", "endocytoscopic imaging", "virtual histology" and "optical biopsy". Only full manuscripts and case reports published in English were included. A total of 29 relevant reports were identified. Endocytoscopy was feasible to detect esophageal squamous cell cancer with sensitivity, specificity and accuracy of 95 %, 84 % and 82 %, respectively. Moreover, EC reached excellent sensitivity and specificity for in-vivo diagnosis of colon polyps (91 % and 100 %, respectively). Other diagnostic applications of EC included diagnosis of Barrett's esophagus, Helicobacter pylori, celiac disease and small cell lung cancer. No serious complications of EC have yet been reported. The authors concluded that endocytoscopy is a safe and effective new endoscopic imaging technique to obtain in-vivo histology and guided biopsies with high diagnostic accuracy. Therefore, endocytoscopy has the potential to facilitate both diagnosis and patient management.

Yeung and Mortensen (2011) stated that conventional white-light endoscopy is currently the gold standard for the detection and treatment of colorectal polyps. However, up to 20 % of polyps may be missed on initial examination, especially flat and small mucosal lesions. These investigators reviewed the literature reporting on the use of new advances in endoscopic visualization. Literature searches were performed on PubMed using the terms "chromoendoscopy", "narrow-band imaging" (NBI), "autofluorescence imaging" (AFI), "Fujinon Intelligent Colour Enhancement" (FICE), "I-Scan colonoscopy", "zoom colonoscopy" and "confocal laser endomicroscopy". They focused on systematic reviews, national guidelines and RCTs written in English. Studies were assessed for methodological quality using QUADAS. Prospective studies assessing new technology were also reviewed. Further publications were identified from reference lists. Chromoendoscopy increases the detection of neoplastic polyps compared with conventional colonoscopy. Narrow-band imaging avoids the use of additional dyes and enhances the vascular network of capillaries surrounding the
crypts, increasing the adenoma detection rate and the ability to distinguish between neoplastic and non-neoplastic lesions. Fujinon Intelligent Color Enhancement, AFI and i-Scan are new developments that improve tissue contrast. Zoom endoscopy may be combined with different modalities to help further characterize colonic lesions. Confocal laser endomicroscopy provides live in-vivo high-resolution optical sections of tissue and may be particularly useful in the surveillance of patients with long-standing ulcerative colitis, reducing the number of random biopsies. The authors concluded that although there is mounting evidence that these new technologies are superior to conventional endoscopy, current guidelines are limited. Moreover, they stated that further large-scale RCTs comparing these modalities in different patient subpopulations are warranted.

In a RCT and meta-analysis of published studies, Sabbagh et al (2011) examined if NBI improve detection of colorectal polyps. Eligible adult patients presenting for screening or diagnostic elective colonoscopy were randomly allocated to undergo conventional colonoscopy or NBI during instrument withdrawal by 3 experienced endoscopists. For the systematic review, studies were identified from the Cochrane Library, PUBMED and LILACS and assessed using the Cochrane risk of bias tool. These investigators enrolled a total of 482 patients (62.5% females), with a mean age of 58.33 years (SD of 12.91); 241 into the intervention (NBI) colonoscopy and 241 into the conventional colonoscopy group. Most patients presented for diagnostic colonoscopy (75.3%). The overall rate of polyp detection was significantly higher in the conventional group compared to the NBI group (RR 0.75, 95% CI: 0.60 to 0.96). However, no significant differences were found in the mean number of polyps (MD -0.1; 95% CI: -0.25 to 0.05), and the mean number of adenomas (MD 0.04 95% CI: -0.09 to 0.17). Meta-analysis of studies (regardless of indication) did not find any significant differences in the mean number of polyps (5 RCT, 2,479 participants; WMD -0.07 95% CI: -0.21 to 0.07; I2 68%), the mean number of adenomas (8 RCT, 3,517 participants; WMD -0.08 95% CI: -0.17 to 0.01; I2 62%) and the rate of patients with at least 1 adenoma (8 RCT, 3,512 participants, RR 0.96 95% CI: 0.88 to 1.04; I2 0%). The authors concluded that NBI does not improve detection of colorectal polyps when compared to conventional colonoscopy.

In a Cochrane review, Nagorni et al (2012) compared standard- or high-definition white light colonoscopy (WLC) with NBI colonoscopy for detection of colorectal polyps. These investigators searched The Cochrane Library, MEDLINE, and EMBASE to August 2011. They scanned bibliographies of relevant publications and wrote to experts for additional trials. Two authors independently applied the inclusion criteria and extracted the data to all potential studies without blinding. Authors extracted data independently. Trials with adequate randomization, allocation concealment, and complete outcome data reporting, as well as without selective outcome reporting or other bias were classified as having a lowest risk of bias. Random-effects and fixed-effect meta-analyses were conducted. These researchers identified 11 randomized trials comparing WLC with NBI for detection of colorectal polyps. A total of 8 randomized trials with 3,673 subjects provided data for the analyses. There was no statistically significant difference between WLC (standard-definition and high-definition pooled) and NBI for the detection of patients with colorectal polyps (6 trials, n = 2,832, RR 0.97, 95% CI: 0.91 to 1.04), patients with colorectal adenomas (8 trials, n = 3,673,
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95 % CI: 0.77 to 1.45, I(2) = 0 %). Number of patients with at least 1 colorectal polyp, or colorectal adenoma was significantly lower in the standard-definition WLC group compared to NBI group in fixed-effect meta-analysis (RR 0.87, 95 % CI: 0.78 to 0.97, I(2) = 78 %; RR 0.87, 95 % CI: 0.77 to 0.99, I(2) = 0 %, respectively), but not significantly different in random-effects meta-analysis (RR 0.86, 95 % CI: 0.68 to 1.10, I(2) = 78 %). There was no statistically significant difference between high-definition WLC and NBI in the number of patients with at least 1 colorectal polyp or colorectal adenoma (RR 1.10, 95 % CI: 0.95 to 1.28; RR 0.87, 95 % CI: 0.77 to 0.99, I(2) = 0 %, respectively). The authors concluded that they could not find convincing evidence that NBI is significantly better than high-definition WLC for the detection of patients with colorectal polyps, or colorectal adenomas. Moreover, they found evidence that NBI might be better than standard-definition WLC and equal to high-definition WLC for detection the patients with colorectal polyps, or colorectal adenomas.

In a meta-analysis, Dinesen and colleagues (2012) examined if use of NBI enhances the detection of adenomas. Meta-analyses were conducted of 7 studies using NBI for adenoma detection rate. MEDLINE, Embase, PubMed, and Cochrane databases were searched by using a combination of the following terms: "colonoscopy", "NBI", and "electronic chromoendoscopy". There was a total of 2,936 patients in the NBI studies. Prospective, randomized trials of NBI versus standard WLC were conducted. These researchers excluded spray chromoendoscopy studies as well as studies of inflammatory bowel disease and polyposis syndromes. Main outcome measures were adenoma and polyp detection rates and the number of polyps and adenomas detected per person. There was no statistically significant difference in the overall adenoma detection rate with the use of NBI or WLC (36 % versus 34 %; p = 0.413 [relative risk 1.06; 95 % CI: 0.97 to 1.16]), and there was no statistically significant difference in polyp detection rate by using NBI or WLC (37 % versus 35 %; p = 0.289 [relative risk 1.22; 95 % CI: 0.85 to 1.76]). When the number of adenomas and polyps per patient was analyzed, no significant difference was found between NBI and WLC (0.645 versus 0.59; p = 0.105 and 0.373 versus 0.348; p = 0.139 [weighted mean difference 0.19; 95 % CI: 0.06 to 0.44], respectively). The authors concluded that NBI did not increase adenoma or polyp detection rates.

Carignan and Yagi (2012) stated that new optical technologies are capable of identifying early pathology in tissues or organs in which cancer is known to develop through stages of dysplasia, including the esophagus, colon, pancreas, liver, bladder, and cervix. These diagnostic imaging advances, together as a field known as optical endomicroscopy, are based on confocal microscopy, spectroscopy-based imaging, and optical coherence tomography (OCT), and function as "optical biopsies," enabling tissue pathology to be imaged in-situ as well as in real time without the need to excise and process specimens as in conventional biopsy and histopathology. Optical biopsy techniques can acquire high-resolution, cross-sectional images of tissue structure on the micron scale through the use of endoscopes, catheters, laparoscopes, and needles. Since the
inception of these technologies, dramatic technological advances in accuracy, speed, and functionality have been realized. The current paradigm of optical biopsy, or single-area, point-based images, is slowly shifting to more comprehensive microscopy of larger tracts of mucosa. With the development of Fourier-domain OCT, also known as optical frequency domain imaging or, more recently, volumetric laser endomicroscopy, comprehensive surveillance of the entire distal esophagus is now achievable at speeds that were not possible with conventional OCT technologies. Optical diagnostic technologies are emerging as clinically useful tools with the potential to set a new standard for real-time diagnosis. New imaging techniques enable visualization of high-resolution, cross-sectional images and offer the opportunity to guide biopsy, allowing maximal diagnostic yields and appropriate staging without the limitations and risks inherent with current random biopsy protocols. However, the ability of these techniques to achieve widespread adoption in clinical practice depends on future research designed to improve accuracy and allow real-time data transmission and storage, thereby linking pathology to the treating physician.

Neumann et al (2012) evaluated the clinical utility of CLE in patients with Crohn's disease (CD) and examined if disease activity can be graded using CLE. Consecutive patients with and without CD were enrolled. The colonic mucosa was examined by standard white-light endoscopy followed by CLE. The features seen on CLE were compared between CD patients and controls. A total of 76 patients with CD were screened, of whom 54 patients were included in the present study. Eighteen patients without inflammatory bowel disease (IBD) served as controls. A significantly higher proportion of patients with active CD had increased colonic crypt tortuosity, enlarged crypt lumen, micro-erosions, augmented vascularization, and increased cellular infiltrates within the lamina propria. In quiescent CD, a significant increase in crypt and goblet cell number was detected compared with controls. Based on these findings, these investigators proposed a Crohn's Disease Endomicroscopic Activity Score (CDEAS) for assessing CD activity in-vivo. The authors concluded that CLE has the potential to significantly improve diagnosis of CD compared with standard endoscopy. These findings should be evaluated in future prospective trials to assess the value of this newly developed CLE score for prediction of disease course and therapeutic responses.

In a randomized controlled trial, Kiesslich et al (2007) evaluated the value of combined chromoendoscopy and endomicroscopy for the diagnosis of intra-epithelial neoplasias. The authors concluded that endomicroscopy based on in-vivo histology can determine if ulcerative colitis lesions identified by chromoscopy should undergo biopsy examination, thereby increasing the diagnostic yield and reducing the need for biopsy examinations. Thus, chromoscopy-guided endomicroscopy may lead to significant improvements in the clinical management of UC.

Buchner et al (2010) noted that probe-based CLE (pCLE) allows in-vivo imaging of tissue at micron resolution. Virtual chromoendoscopy systems, such as Fujinon intelligent color enhancement and narrow band imaging, also have potential to differentiate neoplastic colorectal lesions. The authors concluded that confocal endomicroscopy demonstrated higher sensitivity with similar specificity in classification of colorectal polyps. Moreover, they stated that these new methods
may replace the need for ex-vivo histological confirmation of small polyps, but further studies are needed.

In a feasibility study, Shahid et al (2012a) evaluated the accuracy of pCLE and NBI for prediction of histology. The authors concluded that pCLE demonstrated higher sensitivity in predicting histology of small polyps compared with NBI, whereas NBI had higher specificity. When used in combination, the accuracy of pCLE and NBI was extremely high, approaching the accuracy of histopathology. Together, they may reduce the need for histological examination. However, these researchers stated that further studies are needed to evaluate the role of these techniques, especially in the population-based colon cancer screening.

In a prospective, blind, pilot study, Shahid et al (2012b) estimated and compared the accuracy of virtual chromoendoscopy (VCE) and pCLE for detection of residual neoplastic tissue at the site of prior endoscopic mucosal resection (EMR). The authors concluded that confocal endomicroscopy significantly increased the sensitivity for detecting residual neoplasia after colorectal EMR compared with endoscopy alone. When confocal endomicroscopy is used in combination with VCE, the accuracy is extremely high, and sensitivity approaches that of histopathology. Together, they may reduce the need for histologic examination and allow a highly accurate on-table decision to treat again or not, thus avoiding unnecessary repeat procedures. The main drawbacks of this study were its small sample size, lack of power, involvement of highly experienced pCLE experts.

In a meta-analysis, Wanders et al (2013) established the sensitivity, specificity, and real-time negative predictive value of 3 types of narrowed spectrum endoscopy (NBI, image-enhanced endoscopy [I-scan], and Fujinon intelligent chromoendoscopy [FICE]), CLE, and autofluorescence imaging for differentiation between neoplastic and non-neoplastic colonic lesions. The authors concluded that all endoscopic imaging techniques other than autofluorescence imaging could be used by appropriately trained endoscopists to make a reliable optical diagnosis for colonic lesions in daily practice. Moreover, they stated that further research should be focused on whether training could help to improve negative predictive values.

In a systematic review and meta-analysis, Su et al (2013) assessed the effectiveness of CLE for discriminating colorectal neoplasms from non-neoplasms and its contributing factors. The authors concluded that CLE is comparable to colonoscopic histopathology in diagnosing colorectal neoplasms, and is better in conjunction with conventional endoscopy. An endoscopy-based rather than a probe-based modality would be optimal in the application of CLE. The Centre for Reviews and Dissemination (2014) reviewed the metaanalysis by Su et al. and concluded: “Given the high variation between trials and potential limitations in the methods used to synthesise the data, it is difficult to assess the reliability of the findings and the authors’ conclusions and recommendations for practice should be interpreted with caution.”

Ladabaum et al (2013) prospectively evaluated real-time optical biopsy analysis of polyps with NBI by community-based gastroenterologists. These investigators first analyzed a computerized module to train gastroenterologists (n = 13) in optical biopsy skills using photographs of polyps. Then they evaluated a practice-based learning program for these gastroenterologists (n = 12) that included real-time
optical analysis of polyps in-vivo, comparison of optical biopsy predictions to histopathologic analysis, and ongoing feedback on performance. Twelve of 13 subjects identified adenomas with greater than 90% accuracy at the end of the computer study, and 3 of 12 subjects did so with accuracy greater than or equal to 90% in the in-vivo study. Learning curves showed considerable variation among batches of polyps. For diminutive recto-sigmoid polyps assessed with high confidence at the end of the study, adenomas were identified with mean (95% CI) accuracy, sensitivity, specificity, and negative-predictive values (NPVs) of 81% (73% to 89%), 85% (74% to 96%), 78% (66% to 92%), and 91% (86% to 97%), respectively. The adjusted odds ratio for high confidence as a predictor of accuracy was 1.8 (95% CI: 1.3 to 2.5). The agreement between surveillance recommendations informed by high-confidence NBI analysis of diminutive polyps and results from histopathologic analysis of all polyps was 80% (95% CI: 77% to 82%). The authors concluded that in an evaluation of real-time optical biopsy analysis of polyps with NBI, only 25% of gastroenterologists assessed polyps with greater than or equal to 90% accuracy. The NPV for identification of adenomas, but not the surveillance interval agreement, met the ASGE-recommended thresholds for optical biopsy. Moreover, they stated that better results in community practice must be achieved before NBI-based optical biopsy methods can be used routinely to evaluate polyps.

In a prospective, multi-center study, Repici et al (2103) examined if NBI is able to predict colonoscopy surveillance intervals and histology of distal diminutive polyps according to ASGE criteria. Consecutive patients undergoing colonoscopy in 5 centers were included. Participating endoscopists were required to pass a before-study qualifying examination. Histology of polyps that were less than 10 mm was predicted at NBI and assigned a designation of high or low confidence. Accuracy of high-confidence NBI prediction for polyps less than or equal to 5 mm in predicting surveillance intervals and NPV for adenomatous histology in the recto-sigmoid colon were compared with the ASGE thresholds (90% agreement, 90% NPV). A total of 278 patients (mean age of 63 years; 58% male) were enrolled. At colonoscopy, 574 (97.3%) polyps less than 10 mm (429 less than or equal to 5 mm, 60% adenomatous) were retrieved for histologic analysis. Sensitivity, specificity, positive-predictive value (PPV) and NPV, and accuracy of high confidence-NBI predictions for adenomatous histology in lesions less than or equal to 5 mm were 90%, 88%, 89%, 89%, and 89%, respectively. High-confidence characterization of polyps less than or equal to 5 mm predicted the correct surveillance interval in 92% to 99% of cases, according to the American and European guidelines; NPV of high-confidence NBI for adenomatous histology for the recto-sigmoid colon lesions less than or equal to 5 mm was 92%. The authors concluded that high-confidence prediction of histology for polyps less than or equal to 5 mm appears to be sufficiently accurate to avoid post-polypectomy histologic examination of the resected lesions as well as to allow recto-sigmoid hyperplastic polyps to be left in place without resection. The main drawback of this study was that only experienced endoscopists were included.

An UpToDate review on “Colorectal cancer surveillance in inflammatory bowel disease” (Peppercom and Odze, 2014) states that “Chromoendoscopy involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy. A least one controlled trial suggested that staining with methylene blue enhanced the ability to detect the
extent of inflammatory changes and identify intraepithelial neoplasia in patients
with ulcerative colitis undergoing surveillance. Other studies have suggested that
staining with indigo carmine permitted better detection of dysplasia. The clinical
implications and generalizability of these findings require further clarification ....
Narrow band imaging (NBI) is a high-resolution endoscopic technique that
enhances the fine structure of the mucosal surface without the use of dyes. NBI is
not recommended for surveillance in patients with IBD as it has not demonstrated
a benefit in the detection of dysplasia as compared with white light endoscopy or
chromoendoscopy. In one study that compared the performance of NBI with
chromoendoscopy, 44 patients with colitis of eight years or greater disease
duration underwent screening colonoscopy with NBI, followed by
chromoendoscopy. NBI detected significantly fewer lesions as compared with
chromoendoscopy (102 versus 131); however, most missed lesions were not
dysplastic. NBI also detected fewer dysplastic lesions as compared with
chromoendoscopy (20 versus 23), although the difference was not statistically
significant in this small study”.

Guidelines from the Association of Coloproctology of Great Britain and Ireland
(Willilams, et al., 2013) concluded: “Other methods of surface and lesion
examination, as well as endoscopic staging, are currently research tools or not
currently sufficiently sensitive or specific to be widely recommended . . . Optical
coherence tomography and confocal laser endoscopy (CLE) are being evaluated.
A recent review and meta-analysis of CLE suggests that this modality offers
comparable diagnostic accuracy to colonoscopic histopathology in colorectal
neoplasia [citing Su, et al. 2013]. This offers the possibility of in vivo real-time
optical biopsy in the colorectum. I-Scan is a new modality launched by Pentax
(Hoya Corporation, Japan) to enhance lesions difficult to visualize by WLE. There
is, as yet, little literature on its value in colorectal neoplastic characterization of
malignant change.”

Wu, et al. (2014) reported on a metaanalysis of the accuracy of confocal laser
endomicroscopy in diagnosing BE-associated neoplasia by pooling data of existing
trials. Databases including PubMed, EMBASE, the Cochrane Library, the Science
Citation Index and momentous meeting abstracts were searched and evaluated by
two reviewers independently. Meta-analysis was performed. Pooling data were
conducted in a fixed effect model or a random effects model. Eight studies
involving 709 patients and 4008 specimens were analyzed. In a per-patient
analysis, the pooled sensitivity of CLE for detection of neoplasia was 89% (95%
confidence interval [CI], 0.80-0.95), and the specificity was 75% (95% CI, 0.69-
0.81). The area under the curve under the summary receiver operating
characteristic was 0.9472. In a per-location analysis, the pooled sensitivity of CLE
for detection of neoplasia was 70% (95% CI, 0.65-0.74), and the specificity was
91% (95% CI, 0.90-0.92). The area under the curve under the summary receiver
operating characteristic was 0.9509. The authors stated that CLE is a reasonable,
promising modality for management of patients with BE; more prospective trials
need doing to determine whether it is superior to traditional method in diagnosing
BE-associated neoplasia.

Guidelines from the Society for Thoracic Surgeons (Fernando, et al., 2009) state
that “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 Barrett’s esophagus from the American Gastroenterological Association (Wang, et al., 2008) state that narrow band imaging, autofluorescence imaging, chromoendoscopy, optical coherence tomography, and confocal laser endomicroscopy are promising, but “there is not sufficient evidence at this time to recommend the use of these imaging systems on a routine clinical basis,” More recently, an AGA position statement on Barrett’s esophagus stated that “we suggest against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett’s esophagus at this time.” This was a weak recommendation, based upon low quality evidence.

Guidelines on endoscopy for Barrett’s esophagus from the American Society for Gastrointestinal Endoscopy (ASGE, 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.”

British Society of Gastroenterology guidelines on Barrett’s esophagus (Fitzgerald, et al., 2014) state:"Advanced imaging modalities, such as chromoendoscopy or ‘virtual chromoendoscopy’, are not superior to standard white light endoscopy in Barrett’s oesophagus surveillance and are therefore not recommended for routine use (Recommendation grade A)."

CPT Codes / HCPCS Codes / ICD-9 Codes

There are no specific codes for in vivo analysis of colorectal polyps (chromoendoscopy, endocytoscopy, fiberoptic analysis, multi-band imaging, confocal laser (fluorescent) endomicroscopy narrow-band imaging optical chromocolonoscopy or Optical Biops :

ICD-9 codes not covered for indications in the CPB:

556.0 - 556.9 Ulcerative colitis

ICD-9 codes related to the CPB:

153.0 - 154.9 Malignant neoplasm of colon, rectum, rectosigmoid junction and anus

209.11 - 209.17 Malignant carcinoid tumors of the appendix, large intestine, and rectum

209.50 - 209.57 Benign carcinoid tumors of the appendix, large intestine, and rectum
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211.3 Benign neoplasm of colon
211.4 Benign neoplasm of rectum and anal canal
555.0 - 555.9 Regional enteritis [Crohn's disease]

The above policy is based on the following references:


http://qawww.aetna.com/cpb/medical/data/700_799/0783_draft.html

11/26/2014


50. Peppercorn MA, Odze RD. Colorectal cancer surveillance in inflammatory bowel disease. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014.


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