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Emerging technologies in endoscopic imaging

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Abstract

Endoscopic imaging is in part responsible for the recent drop in deaths from gastrointestinal cancers and also for detecting pre-cancerous and non-cancerous conditions and allowing them to be treated effectively, although techniques are far from perfect. Endoscopic imaging has evolved considerably from fiber optic systems 50 years ago to high resolution and high definition systems used at present. Moreover, image enhancement using filters and processors has led to the technique of 'electronic chromoendoscopy' to visualize mucosal blood vessels and surface pit patterns clearly. Magnification by optical zoom or confocal laser microscopy has enabled real time diagnosis and 'virtual histology'. These techniques have contributed to the early detection, assessment and treatment of various gastrointestinal pathologies. The focus of future research is directed towards molecular targeted imaging.

Introduction

Gastrointestinal cancers account for around 17% of deaths from cancer, and will kill almost 280,000 people in the US alone this year according to estimates from the American Cancer Association. In most cases, these deaths are entirely preventable if they are detected early enough and, in recent years, early detection has improved and death rates have dropped. Endoscopic imaging is in part responsible for this drop and also for detecting pre-cancerous and non-cancerous conditions and allowing them to be treated effectively, although techniques are far from perfect. Recent technological advances offer the hope that early detection of these conditions can be much improved.

The flexible endoscopy technique to visualize the gastrointestinal tract was revolutionized with the advent of fiber optic endoscopes in 1957 by Basil Hirschowitz [1]. The fiber optic systems used multiple optic viewing bundles transmitting light focused on to the face of each fiber by repeated internal reflections. The resulting image constructed at the top of the bundle was viewed by the operator with a focusing lens. The main disadvantage with this technique was the frequent rupture of bundles with repeated use, thus resulting in loss of clarity of images. The introduction of video endoscopy was the next major technological development, which enabled the operator to view real time images on a monitor. This was possible by the advent of charged coupled devices comprising an array of several thousand individual photo cells known as picture elements (pixels). They receive photons reflected back from the mucosal surface and produce electrons in proportion to the amount of light received. The variable levels of charge are sent electronically to a video processor, which transposes this analog information into digital data that is processed to produce an image on a television monitor. The last decade has seen major advancements in the pixel densities of the charged coupled devices, and definition of the monitor, thus enabling us to view the mucosal surface in significantly more detail.

High resolution and magnification endoscopy

Early video endoscopes were equipped with charged coupled devices of approximately 200,000 pixels with a focal length of 1-2 cm from the mucosal surface. These images allow the real time diagnosis of pathology such as inflammation (colitis and gastritis) as well as established cancer; however, it did not allow visualization of more

subtle mucosal abnormalities such as celiac enteropathy and early mucosal neoplasia (dysplasia and intramucosal cancer). Current endoscopes now contain digital chips of up to 1.4 million pixels and the processed high quality images are being displayed on high definition monitors. Endoscopes equipped with a movable lens at the tip of the scope can provide optical magnification up to 150 times, which, in combination with the latest high resolution charged coupled devices, allows greatly enhanced mucosal detail. Pit patterns and vascular architecture can now be appreciated in fine detail, whereby certain characteristics are associated with specific pathology. Consequently, the role of high resolution endoscopy and magnification endoscopy in the diagnosis of epithelial pathology has been investigated over the last few years.

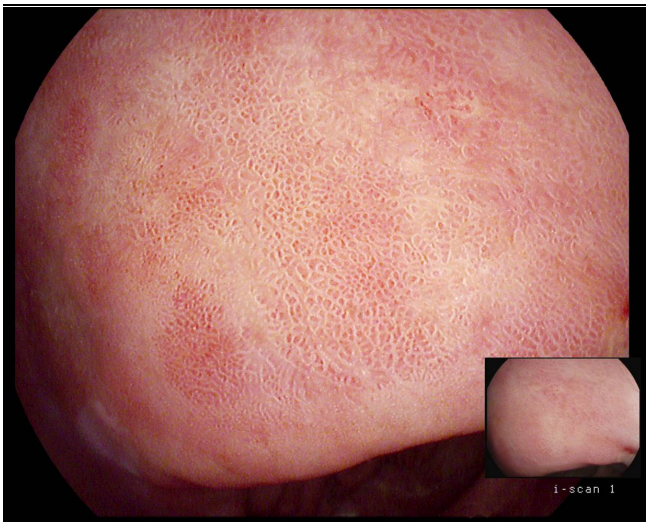
Chromoendoscopy

Many studies have utilised dyes that enhance different aspects of the mucosal pattern. Indigo carmine, for example, concentrates within the grooves or cavities of the mucosa, enhancing the surface architecture and highlighting elevated lesions. Lugol's iodine on the other hand is not taken up by areas of dysplasia within the esophagus. Studies in Barrett's esophagus using high resolution endoscopy, magnification endoscopy and indigo carmine sprayed on the epithelial surface have shown promise in imaging of intestinal metaplasia and dysplasia and patterns in the mucosal architecture correlating with pathology [2,3]. In contrast, application of other agents to the epithelium, such as acetic acid and methylene blue, along with magnification in the diagnosis of dysplasia has shown varying results [4-6]. Promising results were shown using magnification endoscopy to identify gastric atrophy, H. pylori gastritis and celiac disease using magnification in uncontrolled studies [7-10], but magnification endoscopy alone was found to have a modest accuracy in differentiating colonic adenomatous polyps from hyperplastic polyps. However, when magnification endoscopy is combined with chromoscopy, the diagnostic accuracy was significantly better at 90% [11,12].

Electronic chromoendoscopy

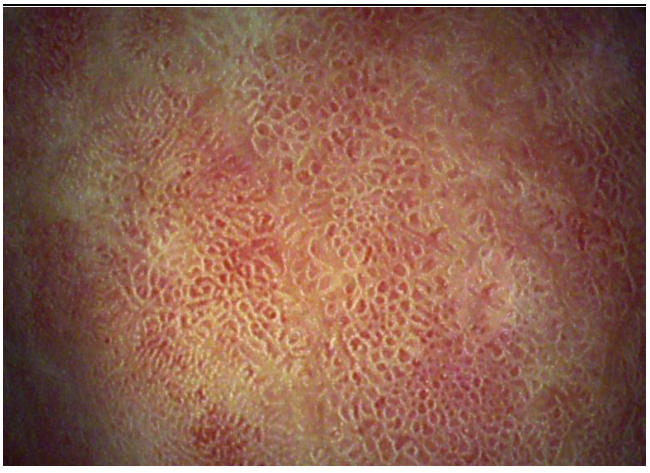
Electronic chromoendoscopy has the advantage of avoiding cumbersome dye spray. Narrow band imaging (Olympus Corporation) uses filter technology to increase the proportion of blue light and narrows the band widths of blue (390-445 nm) and green (530-550 nm) light. The shorter wavelength blue light enhances the mucosal vasculature patterns allowing identification of subtle abnormalities such as enhanced and irregular vasculature, often present in neoplasia and inflammation. Flexible spectral imaging colour enhancement (FICE) (Fujinon endoscopy) and I-Scan (Pentax Medical) are based on a new computed spectral estimation technology (see Figures 1 and 2). These techniques transform an ordinary endoscopic image taken from the video processor and arithmetically process the reflected photons to reconstitute virtual images by increasing the relative intensity of narrowed blue light to a maximum and by decreasing narrowed red and green light to a minimum.

Figure 1. Barrett's dysplasia with i-scan surface enhancement



The image is taken with a Pentax EG2990i gastroecope and an EPKi processor with the addition of I-Scan surface enhancement and demonstrates Barrett's epithelium. There is a glandular and irregular mucosa with coiled vessels and enhanced vasculature in keeping with high grade dysplasia.

Figure 2. Barrett's dysplasia with I-Scan tone enhancement



Use of tone enhancement with I-Scan highlights the vasculature and demonstrates an irregular glandular mucosal pattern with deep grooves and prominent vessels suggestive of Barrett's high grade dysplasia.

Detection of pathology

The studies of narrow band imaging in detecting dysplasia in Barrett's esophagus have yielded conflicting results.

While some of the earlier studies have shown better detection of dysplasia in targeted biopsies than with high resolution endoscopy [13], others have not [14]. However, narrow band imaging appears to be most beneficial in detecting pathology when used by less experienced endoscopists. When applied by experts, the benefit of narrow band imaging was less evident. FICE was found to be comparable to acetic acid chromoscopy in detecting Barrett's dysplasia in a randomized trial [15]. Randomized trials using FICE in colonic adenoma detection failed to show any additional advantage over high resolution endoscopy or conventional chromoscopy [16,17]. However, FICE was noted to improve detection of small bowel lesions compared with capsule endoscopy [18]. High definition colonoscopy with I-Scan was found to be superior to standard video endoscopy in detecting colonic neoplasia [19].

Classification of mucosal pathology

Narrow band imaging with magnification was highly accurate in predicting specialized intestinal metaplasia and high grade dysplasia using the vascular and pit patterns [20]. Narrow band imaging was also found to be useful in differentiating adenomatous polyps from hyperplastic colonic polyps and increasing the yield of polyps in hyperplastic polyposis syndrome *albeit* giving no improvement in adenoma detection rates [21,22]. I-Scan was found to be as accurate as narrow band imaging in classifying small colonic polyps [23], but more accurate in the setting of bowel cancer screening [24].

Trimodal imaging

Commercially available endoscopes combining high resolution chips (high resolution endoscopy), optical magnification, narrow band imaging and autofluorescence imaging facilitate the use of all these image enhancement techniques simultaneously and are often referred to as 'trimodal imaging'. The phenomenon of autofluorescence occurs when a light of shorter wavelength interacts with a tissue containing endogenous fluorophores, which in turn emits light of longer wavelength. A number of biological substances in the gastrointestinal tract, such as collagen and elastin, can act as endogenous fluorophores. Studies in Barrett's esophagus comparing trimodal imaging with standard white light endoscopy in the diagnosis of dysplasia have produced conflicting results. Earlier studies with autofluorescence imaging have produced a high false number of positive results but a good negative predictive value. This has prompted the use of autofluorescence imaging as a 'red flag' technique where the suspicious areas are highlighted in 'magenta' over a background of 'green' and then closely examined with narrow band imaging and magnification endoscopy [25]. A recent randomized trial has shown that trimodal imaging significantly improves the targeted detection of high grade dysplasia and cancer compared with standard white light endoscopy. Subsequent characterization of lesions with narrow band imaging appeared to be of limited value [26]. On the basis of the current available evidence, trimodal imaging does not seem to improve adenoma detection rates, compared with standard endoscopy, and has only modest accuracy in characterizing polyps [27].

Confocal laser endomicroscopy

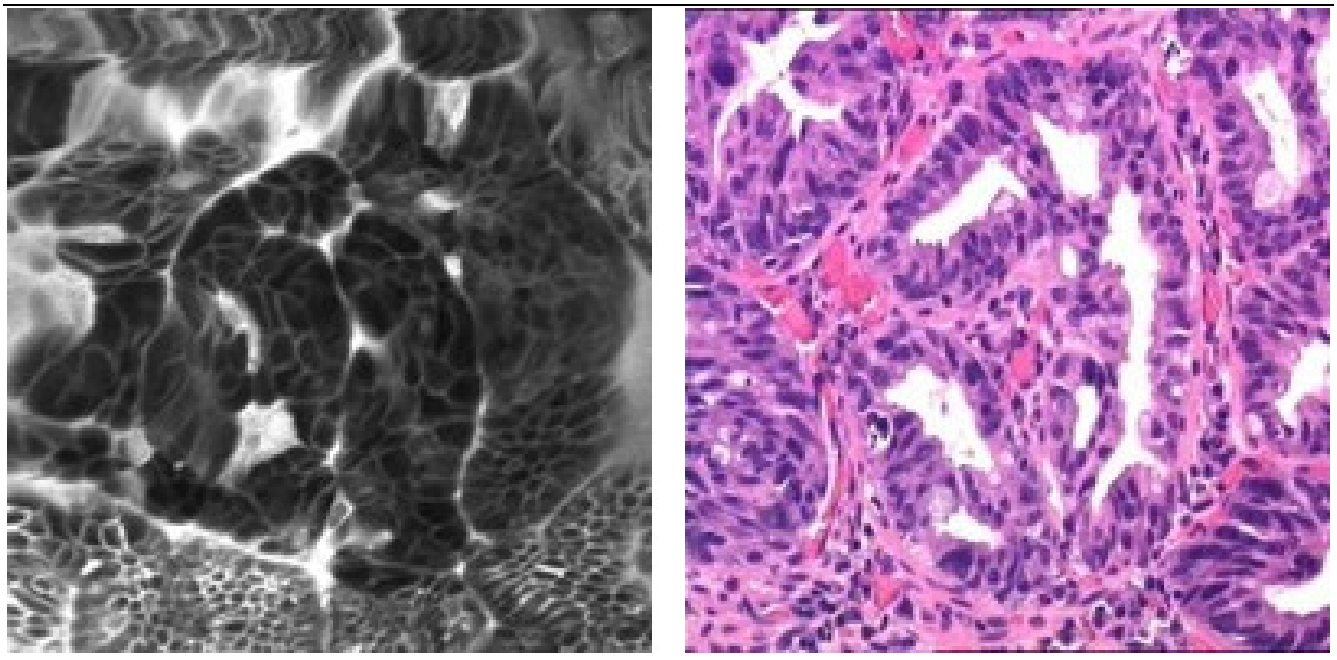
An integrated confocal microscope (Pentax Medical), and a probe-based confocal microscope (Mauna Kea technologies) are available commercially. Blue laser light is focused on the desired tissue after injecting fluorescent materials, which are excited by laser light and the confocal optical unit detects this at a defined horizontal level. Magnification up to 1000 times is obtained with this technology acquiring images at the cellular level, mimicking histopathology sections (Figure 3). Confocal laser endomicroscopy is useful in differentiating gastric metaplasia from intestinal type metaplasia in Barrett's esophagus by identifying the goblet cells (which replace normal epithelial cells in the latter condition) [28]. The sensitivity in predicting intestinal metaplasia and dysplasia in Barrett's esophagus compared with targeted histology was 98% and 93%, with a specificity of 94% and 98% respectively [29]. Confocal laser microscopy has also been used to detect small bowel polyps and large bowel disorders with commendable accuracy. However, this modality demands technical expertise and is time consuming and its use is thus limited to centres of excellence. It is estimated that 200 procedures are necessary before competence is achieved [30]. The system, including a confocal laser endoscope and the processor, costs approximately £90,000 in the UK ($95,000 in the USA).

Optical coherence tomography

Optical coherence tomography (OCT) is an emerging medical imaging technology that relies on the backscattering of light to obtain cross-sectional images of tissue. OCT works on similar principles to ultrasound but uses light waves to quantitatively measure backscattering, which is performed at each axial depth. OCT is generally performed using catheters passed through the working channel of endoscopes. In contrast to endoscopic ultrasound, this does not require a water interface or tissue contact. Images are either linear or radial and are acquired at a depth of 1-2 mm. Real time scanning is possible to acquire high resolution images.

Initial studies have demonstrated that the individual layers of the intestinal wall, including the mucosa,

Figure 3. Matched confocal laser endomicroscopy images of the epithelium and histology. Accredited to Prof. Ralf Kiesslich, Universitätsmedizin, Mainz, Germany



The left image is taken with a Pentax EG3870CIK endomicroscope following fluorescene injection to highlight the vasculature. The cellular architecture can be seen with large nuclei, loss of polarity and fluorescence leakage typical of in-situ carcinoma. The matching right image is an H&E stained histology section demonstrating similar cellular architecture.

submucosa, muscle layers and surrounding connective tissue (adventitia) are distinguishable using this technique. Abnormal tissue layer patterns have been described in various diseases [31]. A prospective biopsy correlated study found that the sensitivity and specificity for diagnosing intramucosal cancer and high grade dysplasia in Barrett's esophagus were 83% and 75%, respectively, using an OCT image scoring system [32]. This technique was also evaluated in small bowel, colon and biliary tract. One study identified features of ulcerative colitis on OCT, which correlated with histology despite the epithelium appearing normal on white light endoscopy [33]. Large randomised studies are necessary to substantiate the use of this emerging technology.

Other emerging technologies

Elastic scattering spectroscopy is a point measurement using an appropriate optical geometry which senses changes in the sub-cellular components and absorption by hemoglobin [34]. This technique uses an optical probe which is passed through the working channel of the endoscope and white light is used from a xenon arc lamp. The backscattered light from the upper layers of the tissue is propagated to the spectrometer. A study in 81 patients with matched optical and histological sites in Barrett's esophagus showed that the sensitivity for detection of high grade dysplasia and cancer was 92% and specificity was 60%. Elastic scattering spectroscopy was also useful in differentiating high risk sites from inflammatory areas with commendable accuracy [35]. The role of this modality in other areas of gastrointestinal tract is less well studied. The current drawback with elastic scattering spectroscopy is that it is limited to point analysis at optical biopsy sites requiring multiple applications in order to assess the whole field.

Raman spectroscopy provides molecular specific tissue information through non-elastically scattered light of a single wavelength light source such as a laser. The Raman signal is often weak, necessitating intensive signal processing for its detection. This technique has been found to be useful in identification and classification of neoplasia in Barrett's esophagus and differentiating hyperplastic and adenomatous colonic polyps [36,37]. However, largely this technique remains a research tool and more studies are necessary to demonstrate its clinical value.

More recently, molecular targeted imaging has been studied. The two most common probes developed thus far are antibodies and peptides. Peptides are smaller in size, easy to label with fluorescent dyes and have rapid binding kinetics with minimal immunogenicity. A recent

Table 1. Summary table for techniques used in Barrett's dysplasia and Barrett's specialised intestinal metaplasia

Condition	Best technique Confocal laser endomicroscopy				Second best technique Electronic chromoendoscopy			
	Estimated cost*	Sensitivity	Specificity	Expertise required	Estimated cost*	Sensitivity	Specificity	Expertise required
Barrett's dysplasia	£90,000 (UK) $ 95,000 (USA)	93%	98%	High [30]	£65,000 (UK) $ 55,000–100,000 (USA)	96%	94%	Medium
Barrett's specialised intestinal metaplasia	£90,000 (UK) $ 95,000 (USA)	98%	94%	High [30]	£65,000 (UK) $ 55,000–100,000 (USA)	95%	65%	Medium

*Pricing varies between countries

study identified a peptide SNFYMPL, which specifically binds to dysplasia in Barrett's esophagus and can be fluorescence labeled to target premalignant mucosa on imaging [38].

Summary

Endoscopic imaging is rapidly evolving and, with the advancement in electronics, high resolution endoscopes with high definition monitors are able to identify subtle mucosal abnormalities. Image enhancement techniques with magnification have enabled us to visualize the mucosal vascular and pit patterns and thus identify early cancerous changes. 'Optical biopsy' techniques such as confocal laser microscopy have not been widely used as they are technically challenging. None of these techniques are specific enough to avoid the need for histopathology sampling and obtaining a real time diagnosis. Nonetheless, they are helpful in targeting abnormal areas and thus help in early diagnosis and endotherapy. Molecularly targeted imaging using labeled peptides is exciting and promising.

The ideal optical system for assessing the gastrointestinal tract is one which enables the user to accurately identify and characterize pathology *in vivo* (see Table 1). In addition, the technology should be easy to use without extensive training, such that it does not present a barrier to its use outside expert centers. In our opinion, there are some technologies which have shown promise in meeting these specifications. Raman spectroscopic mapping, particularly with the introduction of a fiber probe may allow immediate *in vivo* diagnosis of neoplasia. Moreover, the topical application of tumor-targeting Raman nanoparticles enables the user to target specific areas of abnormality as a 'red flag' technique, increasing the sensitivity and accuracy of the technology. The other technology we believe is likely to develop a role in endoscopic imaging is OCT. There has been a marked improvement in the resolution of OCT and the rate of image requisition. Evaluation of tissue microstructure by OCT on combination with fluorescence molecular imaging is likely to yield information not only regarding pathological processes but also vascular microstructure and cellular architecture.

Abbreviations

FICE, Flexible spectral imaging colour enhancement; OCT, Optical coherence tomography.

Competing interests

The authors declare that they have no competing interests

References

1. Hirschowitz Bi, Peters Cw, Curtiss Le: **Preliminary report on a long fiberscope for examination of stomach and duodenum.** *Med Bull (Ann Arbor)* 1957, **23:**178-180.

F1000 Factor 8
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

2. Sharma P, Weston AP, Topalovski M, Cherian R, Bhattacharyya A, Sampliner RE: **Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus.** *Gut* 2003, **52:**24-7.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

3. Sharma P, Marcon N, Wani S, Bansal A, Mathur S, Sampliner R, Lightdale C: **Non-biopsy detection of intestinal metaplasia and dysplasia in Barrett's esophagus: a prospective multicenter study.** *Endoscopy* 2006, **38:**1206-12.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

4. Fortun PJ, Anagnostopoulos GK, Kaye P, James M, Foley S, Samuel S, Shonde A, Badreldin R, Campbell E, Hawkey CJ, Ragunath K: **Acetic acid-enhanced magnification endoscopy in the diagnosis of specialized intestinal metaplasia, dysplasia and early cancer in Barrett's oesophagus.** *Aliment Pharmacol Ther* 2006, **23:**735-42.

5. Guelrud M, Herrera I, Essenfeld H, Castro J, Antonioli DA: **Intestinal metaplasia of the gastric cardia: A prospective study with enhanced magnification endoscopy.** *Am J Gastroenterol* 2002, **97:**584-9.

6. Meining A, Rosch T, Kiesslich R, Muders M, Sax F, Heldwein W: **Inter- and intra-observer variability of magnification chromoendoscopy for detecting specialized intestinal metaplasia at the gastroesophageal junction.** *Endoscopy* 2004, **36:**160-4.

7. Anagnostopoulos GK, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, Foley S, Sunil S, Atherton JJ, Hawkey C, Ragunath K: **High-resolution magnification endoscopy can reliably identify normal gastric mucosa, Helicobacter pylori-associated gastritis, and gastric atrophy.** *Endoscopy* 2007, **39:**202-7.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

8. Gonen C, Simsek I, Sarioglu S, Akpinar H: **Comparison of high resolution magnifying endoscopy and standard videoendoscopy for the diagnosis of Helicobacter pylori gastritis in**

routine clinical practice: a prospective study. *Helicobacter* 2009, **14:**12-21.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

9. Badreldin R, Barrett P, Wooff DA, Mansfield J, Yiannakou Y: **How good is zoom endoscopy for assessment of villous atrophy in coeliac disease?** *Endoscopy* 2005, **37:**994-8.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

10. Cammarota G, Martino A, Pirozzi GA, Cianci R, Cremonini F, Zuccalà G, Cuoco L, Ojetti V, Montalto M, Vecchio FM, Gasbarrini A, Gasbarrini G: **Direct visualization of intestinal villi by high-resolution magnifying upper endoscopy: a validation study.** *Gastrointest Endosc* 2004, **60:**732-8.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

11. East JE, Suzuki N, Saunders BP: **Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study.** *Gastrointest Endosc* 2007, **66:**310-6.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

12. Hurlstone DP, Cross SS, Adam I, Shorthouse AJ, Brown S, Sanders DS, Lobo AJ: **Efficacy of high magnification chromoscopic colonoscopy for the diagnosis of neoplasia in flat and depressed lesions of the colorectum: a prospective analysis.** *Gut* 2004, **53:**284-90.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

13. Wolfsen HC, Crook JE, Krishna M, Achem SR, Devault KR, Bouras EP, Loeb DS, Stark ME, Woodward TA, Hemminger LL, Cayer FK, Wallace MB: **Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's Esophagus.** *Gastroenterology* 2008, **135:**24-31.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

14. Kara MA, Peters FP, Rosmolen WD, Krishnadath KK, ten Kate FJ, Fockens P, Bergman JJ: **High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study.** *Endoscopy* 2005, **37:**929-36.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

15. Pohl J, May A, Rabenstein T, Pech O, Nguyen-Tat M, Fissler-Eckhoff A, Ell C: **Comparison of computed virtual chromoendoscopy and conventional chromoendoscopy with acetic acid for detection of neoplasia in Barrett's esophagus.** *Endoscopy* 2007, **39:**594-8.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

16. Chung SJ, Kim D, Song JH, Park MJ, Kim YS, Kim JS, Jung HC, Song IS: **Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates.** *Gastrointest Endosc* 2010, **72:**136-42.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

17. Pohl J, Lotterer E, Balzer C, Sackmann M, Schmidt KD, Gossner L, Schaab C, Frieling T, Medve M, Mayer G, Nguyen-Tat M, Ell C: **Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial.** *Gut* 2009, **58:**73-8.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

18. Imagawa H, Oka S, Tanaka S, Noda I, Higashiyama M, Sanomura Y, Shishido T, Yoshida S, Chayama K: **Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy.** *Gastrointest Endosc* 2011, **73:**299-306.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

19. Hoffman A, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S *et al.*: **High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial.** *Endoscopy* 2010, **42:**827-33.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

20. Mannath J, Subramanian V, Hawkey CJ, Ragunath K: **Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis.** *Endoscopy* 2010, **42:**351-9.

21. Boparai KS, van den Broek FJ, van ES, Fockens P, Dekker E: **Increased polyp detection using narrow band imaging compared with high resolution endoscopy in patients with hyperplastic polyposis syndrome.** *Endoscopy* 2011, **43:**676-82.

22. Rastogi A, Early DS, Gupta N, Bansal A, Singh V, Ansstas M, Jonnalagadda SS, Hovis CE, Gaddam S, Wani SB, Edmundowicz SA, Sharma P: **Randomized, controlled trial of standard-definition white-light, high-definition white-light, and narrow-band imaging colonoscopy for the detection of colon polyps and prediction of polyp histology.** *Gastrointest Endosc* 2011, **74:**593-602.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

23. Lee CK, Lee SH, Hwangbo Y: **Narrow-band imaging versus I-Scan for the real-time histological prediction of diminutive colonic polyps: a prospective comparative study by using the simple unified endoscopic classification.** *Gastrointest Endosc* 2011, **74:**603-9.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

24. Banks M, Haidry R, Whitley L, Stein J, Langmead L, Bloom S, O'Bichere A, McCartney S, Basherdas K, Rodriguez-Gusto M, Lovat L: **Polyp detection is improved by megapixel white light high resolution colonoscopy in the uk national bowel cancer screening program.** Presented at Annual Meeting on British-Society-of-Gasenterology: 2011, **In press**.

25. Hoffman A, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S, Galle PR, Neurath MF, Kiesslich R: **Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system.** *Gut* 2008, **57:**167-72.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

26. Curvers WL, Herrero LA, Wallace MB, Wong Kee Song LM, Ragunath K, Wolfsen HC, Prasad GA, Wang KK, Subramanian V, Weusten BL, Ten Kate FJ, Bergman JJ: **Endoscopic tri-modal imaging is more effective than standard endoscopy in identifying early-stage neoplasia in Barrett's esophagus.** *Gastroenterology* 2010, **139:**1106-14.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

27. Kuiper T, van den Broek FJ, Naber AH, van Soest EJ, Scholten P, Mallant-Hent RCh, van den Brande J, Jansen JM, van Oijen AH, Marsman WA, Bergman JJ, Fockens P, Dekker E: **Endoscopic**

trimodal imaging detects colonic neoplasia as well as standard video endoscopy. *Gastroenterology* 2011, **140:**1887-94.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

28. Gheorghe C, Iacob R, Becheanu G, Dumbrav AM: **Confocal endomicroscopy for in vivo microscopic analysis of upper gastrointestinal tract premalignant and malignant lesions.** *J Gastrointestin Liver Dis* 2008, **17:**95-100.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

29. Kiesslich R, Gossner L, Goetz M, Dahlmann A, Vieth M, Stolte M, Hoffman A, Jung M, Nafe B, Galle PR, Neurath MF: **In vivo histology of Barrett's esophagus and associated neoplasia by confocal laser endomicroscopy.** *Clin Gastroenterol Hepatol* 2006, **4:**979-87.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

30. Neumann H, Vieth M, Atreya R, Neurath MF, Mudter J: **Prospective evaluation of the learning curve of confocal laser endomicroscopy in patients with IBD.** *Histol Histopathol.* 2011, **26:**867-72.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

31. Sivak MV Jr, Kobayashi K, Izatt JA, Rollins AM, Ung-Runyawee R, Chak A, Wong RC, Isenberg GA, Willis J: **High-resolution endoscopic imaging of the GI tract using optical coherence tomography.** *Gastrointest Endosc* 2000, **51:**474-9.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

32. Evans JA, Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, Lauwers GY, Mino-Kenudson M, Nishioka NS, Tearney GJ: **Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus.** *Clin Gastroenterol Hepatol* 2006, **4:**38-43.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

33. Familiari L, Strangio G, Consolo P, Luigiano C, Bonica M, Barresi G, Barresi V, Familiari P, D'Arrigo G, Alibrandi A, Zirilli A, Fries W, Scaffidi M: **Optical coherence tomography evaluation of ulcerative colitis: the patterns and the comparison with histology.** *Am J Gastroenterol* 2006, **101:**2833-40.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

34. Lovat L, Bown S: **Elastic scattering spectroscopy for detection of dysplasia in Barrett's esophagus.** *Gastrointest Endosc Clin N Am* 2004, **14:**507-17, ix.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

35. Lovat LB, Johnson K, Mackenzie GD, Clark BR, Novelli MR, Davies S, O'Donovan M, Selvasekar C, Thorpe SM, Pickard D, Fitzgerald R, Fearn T, Bigio I, Bown SG: **Elastic scattering spectroscopy accurately detects high grade dysplasia and cancer in Barrett's oesophagus.** *Gut* 2006, **55:**1078-83.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

36. Kendall C, Stone N, Shepherd N, Geboes K, Warren B, Bennett R *et al.*: **Raman spectroscopy, a potential tool for the objective identification and classification of neoplasia in Barrett's oesophagus.** *J Pathol* 2003, **200:**602-9.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012

37. Molckovsky A, Song LM, Shim MG, Marcon NE, Wilson BC: **Diagnostic potential of near-infrared Raman spectroscopy in the colon: differentiating adenomatous from hyperplastic polyps.** *Gastrointest Endosc* 2003, **57:**396-402.

F1000 Factor 6
Evaluated by Jayan Mannath and Matthew Banks 16 Jan 2012

38. Li M, Anastassiades CP, Joshi B, Komarck CM, Piraka C, Elmunzer BJ, Turgeon DK, Johnson TD, Appelman H, Beer DG, Wang TD: **Affinity peptide for targeted detection of dysplasia in Barrett's esophagus.** *Gastroenterology* 2010, **139:** 1472-80.

F1000 Factor 6
Evaluated by Matthew Banks 16 Jan 2012