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# Advances in the Diagnosis and Management of Inflammatory Bowel Disease: Challenges and Uncertainties

Mahmoud Mosli,[1,2] Mohammad Al Beshir,[2,3] Bandar Al-Judaibi,[2,4] Turki Al-Ameel,[3,5] Abdulaziz Saleem,[6,7] Talat Bessissow,[8] Subrata Ghosh,[9] and Majid Almadi[4,8]

[1]Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Medicine, London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada
[3]Department of Medicine, King Fahd Specialist Hospital, Dammam, Saudi Arabia
[4]Department of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia
[5]Department of Medicine, University of Alberta, Edmonton, Canada
[6]Department of Surgery, McGill University and McGill University Health Centre, Montreal, Canada
[7]Department of Surgery, King Abdulaziz University, Jeddah, Saudi Arabia
[8]Department of Medicine, McGill University and McGill University Health Centre, Montreal, Canada
[9]Department of Medicine, University of Calgary, Calgary, Canada
**Address for correspondence:** Dr. Mahmoud Mosli E-mail: majid.almadi@gmail.com

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## Abstract

Over the past two decades, several advances have been made in the management of patients with inflammatory bowel disease (IBD) from both evaluative and therapeutic perspectives. This review discusses the medical advancements that have recently been made as the standard of care for managing patients with ulcerative colitis (UC) and Crohn's Disease (CD) and to identify the challenges associated with implementing their use in clinical practice. A comprehensive literature search of the major databases (PubMed and Embase) was conducted for all recent scientific papers (1990–2013) giving the recent updates on the management of IBD and the data were extracted. The reported advancements in managing IBD range from diagnostic and evaluative tools, such as genetic tests, biochemical surrogate markers of activity, endoscopic techniques, and radiological modalities, to therapeutic advances, which encompass medical, endoscopic, and surgical interventions. There are limited studies addressing the cost-effectiveness and the impact that these advances have had on medical practice. The majority of the advances developed for managing IBD, while considered instrumental by some IBD experts in improving patient care, have questionable applications due to constraints of cost, lack of availability, and most importantly, insufficient evidence that supports their role in improving important long-term health-related outcomes.

**Keywords:** Advancements, Crohn's disease, diagnosis, management, review, treatment, update, ulcerative colitis

Inflammatory bowel disease (IBD) includes both ulcerative colitis (UC) and Crohn's disease (CD). Patients with IBD commonly follow a lifelong relapsing and remitting course that can affect their quality of life and result in long-term sequelae.[1,2,3,4] Optimized medical care and collaboration between different health care providers can potentially prevent such complications.[5,6,7,8]

UC is limited to the superficial layers of the large bowel, with a tendency toward involving the distal part.[9,10] Untreated UC can lead to uncontrolled gastrointestinal (GI) bleeding, toxic megacolon, or, with long-term unmanaged disease, colorectal cancer (CRC).[11,12] As UC is limited to the colon, failure of medical treatments, including oral and/or rectal anti-inflammatory drugs, immunomodulators, or biologic agents, among other reasons, is an indication for pursuing a surgical intervention in the form of colectomy

with the formation of an ileal pouch anal anastomosis (IPAA) or an end-ileostomy.[13,14,15] Although removing the colon is considered a cure for UC, pouchitis (inflammation in the pouch) is a frequently occurring complication that causes significant morbidity and requires further management.[16]

In distinction, CD can involve any part of the GI tract and can present in a penetrating (fistulizing), fibrostenotic (stricturing), or inflammatory pattern, and usually has a clinical presentation of diarrhea, abdominal pain, and malnutrition.[17,18,19] Surgical resection of the affected bowel segments is a short-term solution that is rarely curative and in the long run can lead to detrimental complications such as short gut syndrome and total parenteral nutrition (TPN) dependency.[20,21] Evaluative tools that can assess proximal segments of the small bowel that are beyond the reach of standard ileocolonoscopy are important and can provide optimal assessments that are vital in taking the decision of proceeding with surgery.[22,23,24] As endoscopic assessment can be associated with complications related to sedation or colonic perforation, noninvasive methods to detect disease activity are needed.[25] Furthermore, both UC and CD are associated with a wide range of extraintestinal manifestations such as sclerosing cholangitis, spondyloarthropathy, and metabolic bone disease, which ideally should be handled by specialized physicians.[26] Additionally, novel drugs that have been proven effective and safe in treating UC and CD are being introduced as a replacement or compliment for conventional therapies that are either ineffective or known to be associated with adverse events.[27] Collectively, these clinical aspects of IBD suggest that advances in the continuous and comprehensive care for IBD patients are necessary. However, whether these advancements would impact the overall outcome of IBD patients remains unclear.

The purpose of this narrative review is to discuss the different diagnostic and therapeutic advancements that have recently been introduced into clinical practice to improve the overall care of patients with IBD and to highlight the limitations and challenges associated with their use.

## MATERIALS AND METHODS

A comprehensive search of all major medical literature databases including PubMed, Medline, and Embase was initially conducted using relevant keywords including inflammatory bowel disease, ulcerative colitis, Crohn's disease AND advances, medical care, cost-effectiveness, diagnosis, evaluation, testing, radiology, treatment, therapy, randomized controlled trials (RCTs), surgery, and endoscopy. Subsequently, a separate search strategy was used to perform a more focused search for each section using any additional relevant keyword. Inclusion was not restricted to English papers and effort was made to translate any relevant non- English paper. All retrospective studies, observational cohort studies, case control studies, RCTs, meta-analyses, and systematic reviews discussing the topic of interest were included as sources of data. A different single author performed data extraction for each section, in addition to the primary author (MM). Results were compared and conflicts were resolved by consensus.

## RESULTS

### Diagnosing IBD

**The challenge of early diagnosis** The diagnosis of CD can be challenging, particularly if the disease is limited to the small bowel. In practice, it is not uncommon that patients report having complained of GI symptoms for months to years prior to their diagnosis. This delay can be explained by patient-centered factors as well as lack of available resources. CD is often mistaken for irritable bowel syndrome (IBS) or food intolerances because of the vague and overlapping symptoms occurring mainly at a young age.[28] Furthermore, the limited access to a gastroenterologist and resources results in a deferral of several months until a diagnosis is reached,[29,30] and this potentially leads to earlier disease-related complications.

Recent advances in abdominal imaging, such as magnetic resonance (MR) imaging and computed tomographic enterography (CTE), as well as in endoscopic imaging, such as small bowel enteroscopy (SBE), should constitute adjunct investigational means to standard ileocolonoscopy. Both MR and CTE are currently considered key investigations in the diagnosis, follow-up of disease activity, and identification of complications.[31] Once the diagnosis is entertained, early detection is essential to allow better disease prognostication as well as rapid control of inflammation to prevent complications. In fact, long-term follow-up of anti-tumor necrosis factor (anti-TNF) TNF studies such as Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) and EXTEND demonstrates that early

introduction of adalimumab (ADA) provides significantly higher rates of clinical remission,[32,33] but there is a paucity of studies which show that early diagnosis of IBD prevents long-term complications.

## Diagnostic and evaluative advances

**Serological markers** There are numerous serological markers that have been identified and are associated with IBD. These have been used in the discrimination between IBD and IBS, identifying the subtypes of IBD and phenotypes of CD, prognostication of disease, and in predicting the disease course and the need for surgery in both adult and pediatric populations. Some of these markers include antibodies to the outer membrane porin of *Escherichia coli* (OmpC-IgG), *Pseudomonas fluorescens* (anti-I2), and flagellin (anti-CBir1). While the anti-glycan antibodies include anti-*Saccharomyces cerevisiae* (ASCA), antilaminaribioside (ALCA), anti-chitobioside (ACCA), anti-mannobioside (AMCA), anti-laminarin (anti-L), and anti-chitin (anti-C) antibodies. The majority of these antibodies have been associated with CD, while UC has been associated with anti-neutrophil cytoplasmic autoantibodies (pANCA), antibodies against goblet cells (GAB),[34] anti-proteinase 3 (anti-PR3),[35] and high mobility group box 1 and box 2 non-histone chromosomal proteins (HMGB1 and HMGB2) which have been described as novel antigens of pANCA.[36] The utility of serological markers associated with IBD in clinical practice remains uncertain and is limited mainly to the academic institutes where research is the main drive behind ordering them. They include the following.

*Predicting the development of IBD*: Data from the international European Prospective Investigation into Cancer and Nutrition (EPIC)[37] study that enrolled more than 520,000 individuals demonstrated that the combination of the serological markers pANCA, ASCA, anti-CBir1, and anti-OmpC was able to predict the development of CD (area under the curve 0.68) and UC (area under the curve 0.66) in individuals who were considered to be at low risk.[37] Additionally, the predictive value of these markers increased as the time to the diagnosis of IBD was shorter,[37] but the use of these markers to differentiate between IBD and IBS, which can be clinically relevant, is not well studied.

*Differentiation between CD and UC*: The discrimination between CD and UC based on clinical, endoscopic, and histological manifestations can be challenging in certain cases, such as preoperatively in cases requiring colectomy and IPAA formation. Therefore, there is a need for the biomarkers that would differentiate between both. There are numerous attempts at using the currently known serological markers or a combination of these markers to separate CD from UC,[38] as well as attempts of finding new biomarkers.[39] In a recent meta-analysis, ASCA was able to discriminate between CD and UC with a sensitivity of 56.6% [95% confidence interval (CI) 51.9-61.3%], specificity of 88.1% (95% CI 85.8-90.0%], and a diagnostic odds ratio (OR) of 10.2 (95% CI 7.7-13.7).[38]

*Predicting the disease course and the phenotype*: A meta-analysis by Kaul *et al*.[38] found those who were ASCA positive developed stricturing or penetrating/fistulizing phenotype of CD with a sensitivity of 70.8% and specificity of 48.5%, while ACCA had the highest specificity of 75.1% but a lower sensitivity (43.3%),[38] and a diagnostic OR of 2.7 (95% CI 2.0-3.6). The same systematic review found that with increasing number of positive anti-glycan markers, there was a more aggressive disease course as well as the need for surgery.[38] Apart from ASCA, which was found to be associated with ileal and ileo-colonic location of CD, the remainder of the anti-glycan markers varied in their association with disease location.[38] A meta-analysis by Zhang *et al*.[40] found that an ASCA-positive status had a higher risk of early-onset CD (OR 2.25, 95% CI 1.41-3.57), ileal involvement disease (OR 1.70, 95% CI 1.05-2.77), complicated disease behavior (OR 2.09, 95% CI 1.71-2.57), perianal disease (OR 1.49, 95% CI 1.14-1.94), and the risk of surgery (OR 1.61, 95% CI 1.29-2.01).[40]

In a pediatric cohort of 796 patients with CD with a median age at diagnosis of 12 years and median disease duration of 32 months, an increasing frequency of penetrating and structuring phenotypes was found for those with a positive anti-OmpC [hazard ratio (HR) 2.4, 95% CI 1.2-4.9] and anti-CBir1 (HR 2.5, 95% CI 1.2-5.2), while it decreased for those with a positive pANCA (HR 0.16, 95% CI 0.04-0.70). The need for surgery also increased with ASCA-positive status (HR 3.2, 95% CI 1.1-9.5) and anti-OmpC–positive status (HR 2.2, 95% CI 1.3-3.8). There was also an increasing trend with increasing antibody sum and quartile sum score to these antibodies.[41] More studies are required to clarify whether or not the use of these markers can be generalized to predict the disease course and future severity.

**Genetic markers** Genetics, in addition to environmental factors and an altered immune response, not only constitutes the etiology for IBD but also plays a role in the phenotype as well as disease progression.[41] In order to perform a genetic assessment, a geneticist and access to performing genetic testing are needed. There are many shared loci between immune-mediated inflammatory disorders,[42] as well as between UC and CD.[43,44] Multiple functional polymorphisms of the interferon regulatory factor 5 (*IRF5*) gene are associated with systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, multiple sclerosis, psoriasis, and IBD.[42] *IRF5* polymorphisms were found to affect the risk profile for CD and UC in conjunction with ancestry and nucleotide oligomerization domain 2 (NOD2) genotypes.[42] A meta-analysis found no association between NOD1/caspase recruitment domain-containing protein (CARD) 4 insertion–deletion polymorphism and IBD in general, but there was an association between NOD1/CARD4 insertion–deletion polymorphism and IBD at a young age (<40 years).[45] Multiple studies have demonstrated an association between the genotype of patients and the development of anti-glycan markers,[38,46] where a CARD15 variant in CD was associated with an increased probability of being ASCA and ALCA positive (66% and 43%, respectively),[46] as well as a higher titer of ASCA.[46,47] Also, the use of a panel of serological markers in addition to genetic markers [autophagy-related 16-like 1 (ATG16L1), the NK-2 homeobox NKX2-3, extracellular matrix protein-1 (ECM1), and signal transducer and activator of transcription 3 (STAT3)] and inflammatory markers, when compared to serological markers only, increased the accuracy of discrimination between IBD and non-IBD patients (area under the curve from 80% to 86%, $P < 0.001$) as well as between UC and CD (area under the curve from 78% to 93%, $P < 0.001$).[48] A second study demonstrated that patients with single nucleotide polymorphism (SNP) 13 NOD2 risk alleles experienced increased complications versus patients without NOD2 mutations.[49] Also, a model that combined serological as well as genetic markers could predict the complications in patients with CD.[49] The challenges associated with the use of genetic markers in IBD range from cost to limited application, as these markers have so far not been found to be useful in screening the family members of IBD patients and are generally thought to be not ready for primetime.

**Noninvasive inflammatory markers** Non-invasive markers of inflammation have become an important part of the daily assessment of patients with IBD. The use of these markers has expanded to include making initial diagnosis and differentiating between IBD and other diseases, evaluating the symptoms of active IBD to rule out flare-ups, postoperative evaluation, monitoring the response to therapy, and predicting relapse.[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64] Historically, inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were used for these indications, but have since fallen out of favor as they are generally non-specific.[65] More recently, markers of inflammation that are specific to the GI tract, such as fecal calprotectin (FC) and stool lactoferrin (SL), have been introduced.

*Stool lactoferrin*: Lactoferrin is an iron-binding glycoprotein stored in the secretory granules of neutrophils. It can be detected in stool in the setting of a local inflammatory response as it is released by most mucosal surfaces, including those of the small and large bowel.[66,67,68] SL has been proven to be a useful tool to diagnose IBD in patients presenting with lower GI symptoms[69] and to differentiate between active and inactive disease,[70,71] especially in the pediatric population.[64,72] Furthermore, SL has been found to correlate well with the endoscopic severity of colonic IBD (Pearson's $r = 0.9$, $P = 0.001$) [73,74,75] and to have high positive predictive value (PPV; 100%) and negative predictive value (NPV; 83%) for diagnosing small bowel CD,[76] but the inherent variability seen with endoscopic grading of severity in UC can argue against the validity of this correlation. Further, the correlation between SL and mucosal healing and disease recurrence remains unknown. Even though SL is easy to perform and relatively inexpensive compared to endoscopic or radiological methods used in this clinical context, it is still not readily available in many parts of the world.

*Fecal calprotectin*: Calprotectin (previously called L1 protein) is a protein with antimicrobial properties and is released by white blood cells and squamous cells in response to inflammation.[77,78] FC has the advantage of stability in the stool for up to 1 week, as it is resistant to proteolytic enzymes and heat.[79,80] The role of FC in managing IBD is not well established. FC is a sensitive marker of gut inflammation as it correlates well with fecal excretion of indium-111–labeled neutrophilic granulocytes, the gold standard of disease activity.[81] It also accurately predicts the disease severity[82] as well as clinical relapse after infliximab treatment in UC patients,[83] and has been used as a monitoring tool in clinical trials.[84,85] As

FC is easy to perform and results can be rapidly provided at the bedside, it serves as a useful and reliable tool for screening symptomatic patients and triaging them accordingly;[86,87] but despite being relatively inexpensive, FC is still not widely available. Although in many specialized centers FC has replaced the repetitive need for endoscopic evaluation in many clinical settings, studies that directly correlate FC levels and endoscopic remission are needed.

## Diagnostic imaging

The role of imaging in the diagnosis of IBD continues to evolve. It has the advantages of simultaneously examining different parts of the GI tract, assessing areas of the bowel that are beyond the reach of the conventional ileocolonoscopy, detecting extraluminal involvement and complications of IBD, and potentially helping in the differentiation between UC and CD. This may lead to better therapeutic decisions, overall patient care and medical education. However, thus far, no single imaging modality has effectively replaced a detailed endoscopic evaluation and histopathologic diagnosis. For many decades, small bowel follow through (SBFT) was considered the imaging modality of choice for the examination of parts of the small bowel that are unreachable by endoscopy.[88] However, with the advancements and accumulating experience with other cross-sectional imaging modalities, the moderate risk of radiation associated with SBFT, and the frequently reported missed ulcers, erosion, and polyps, SBFT has fallen out of favor.[89] It is noteworthy to mention that the long-term significance of detecting such lesions is not fully understood and implementing the use of alternative expensive modalities is, therefore, controversial. The operating characteristics of these modalities have been described with wide variability [Table 1].

**MR imaging** MR is currently the most attractive imaging modality of choice and is a very promising investigatory tool for patients with IBD, particularly in the adult population. It is noninvasive and lacks the burden of ionized radiation, which makes it very suitable for IBD patients given the lifelong remitting/relapsing course of the disease that typically requires repeated examinations. MR can be performed with limited bowel preparation and patients usually receive both oral and intravenous contrast media. Oral neutral contrast medium is provided to help distend the bowel lumen and allows its optimal distinction from the bowel wall. It can be given orally (enterography) or through a naso-enteric tube inserted under fluoroscopic guidance (enteroclysis). MR enteroclysis ensures more consistent luminal distension than simple MR enterography, and is more accurate in detecting early disease, particularly in the jejunum.[90,91,92] However, the sensitivity of enterography in the detection of active disease in the ileum is similar to that of enteroclysis.[93,94] For superficial, subtle mucosal abnormalities, conventional enteroclysis and capsule endoscopy are more accurate than MR imaging.[95,96,97] However, the clinical significance of this finding is yet to be determined and is unlikely to influence the choice of therapy[98] [Figure 1].

The accuracy of MR imaging in CD has been extensively studied, with the reported sensitivity and specificity ranging from 88% to 98% and from 78% to 100%, respectively.[99,100,102] However, the sensitivity of MR colonography in detecting colonic inflammation is low.[103] In a study using conventional colonoscopy as the gold standard, the sensitivity of correctly identifying inflammation on per-segmental analysis of the colon was 31.6% for CD and 58.8% for UC.[104]

The role of MR in detecting intestinal stricturing in CD is important. MR can distinguish between inflammatory and fibrostenotic stricturing and, hence, can guide and alter the treatment decision, as obstruction secondary to active inflammatory disease can be treated medically whereas fibrostenotic obstruction with prestenotic dilatation requires surgical intervention.[105,106] In addition, MR can identify extraluminal findings related to CD, such as lymphadenopathy, fistulas, and abscess, with a high accuracy rate reaching 100% in many studies and is considered the diagnostic imaging of choice for the evaluation of perianal CD.[107,108]

MR enteroclysis can be used as the initial and follow-up examination in both adults and pediatric patients suspected of having CD because it allows accurate assessment of both the proximal and distal small bowel.[91] The main drawbacks to MR studies are their high cost, long patient waiting time, prolonged examination time, and limited availability, particularly in the developing countries.

**Computed tomographic enterography** CTE and enteroclysis have similar principles to MR modalities, which involve ingestion of neutral contrast medium to distend the small bowel followed by CT imaging of

the abdomen. It has an accuracy equal to Magnetic Resonance Enterography (MRE) in the detection of disease activity and bowel damage in CD [localization of CD ($P = 1.0$), bowel wall thickening ($P = 1.0$), bowel wall enhancement ($P = 1.0$), and entero-enteric fistulas ($P = 0.08$)], as well as extraluminal complications, particularly intra-abdominal abscess, but is less suitable than MR in depicting intestinal strictures as well as fistulae and/or sinus tracts.[109,110]

CT is a widely used evaluative tool in the United States for patients with known or suspected IBD, particularly in acute and emergency settings, due to its availability and shorter examination time, but superficial ulcerations are not accurately visualized on CT. This resulted in the recommendation against using CT as a first-line examination in patients suspected of having mild disease.[98] Moreover, due to the significant radiation exposure and the rapid advances in other radiation-free modalities such as MR, US, and capsule endoscopy, the role of CT in IBD patients should be limited only to situations where an emergency evaluation is needed, especially when surgical intervention is likely.

**Small bowel ultrasound** Ultrasonography (US) is a very safe and inexpensive imaging modality that can detect small bowel abnormalities particularly [Figure 2]. US can be used as the first-line imaging procedure in patients with a low suspicion of IBD, particularly pediatric and young adults, as the absence of bowel wall thickening has a good NPV for IBD.[111] However, US can fail to detect superficial lesions and has a low accuracy for evaluating deep intestinal loops and structures (sensitivity = 26.4%, specificity = 98.6%).[112]

One of the main limitations of US is that its diagnostic accuracy in CD is highly dependent on the level of experience of the radiologist as well as the location of disease, with lower accuracy for the disease proximal to the terminal ileum with a missed rate of up to 67%.[113]

Moreover, due to its deep pelvic location, abnormalities in the recto-sigmoid colon can be missed, making evaluation in UC using US less suitable.[113] In the hand of an experienced radiologist, the reported sensitivity of US for the detection of IBD in patients suspected of having the disease varies from 76% to 92%.[114] In patients who have confirmed disease, the reported sensitivity values are even higher (sensitivity 87.3-98%).[98,115] Additionally, US has a very high diagnostic accuracy for the detection of complications related to CD, including strictures (sensitivity = 100%, specificity = 91%), fistulae (sensitivity = 87%, specificity = 90%), and/or abscesses (sensitivity = 100%, specificity = 92%).[116] Furthermore, the use of Color Doppler US and contrast-enhanced US permits the differentiation between inflammatory and fibrostenotic strictures.[117] Therefore, US can be recommended in the follow-up of both symptomatic and asymptomatic CD patients.[118] For US to be considered a standard for assessing patients with IBD, further correlation between US, CTE, MRE, and SBFT is needed to further characterize its performance properties. The challenge of properly training gastroenterologists and radiologists to perform US with high accuracy should also be considered. The strategy of training gastroenterologists to perform reliable US examinations at the bedside has been adopted in Europe.

## Endoscopic advances

**Capsule endoscopy** In 2001, wireless capsule endoscopy (WCE) was approved by the United States Food and Drug Administration (FDA). Generally, WCE should be ordered after ileocolonoscopy, and cross-sectional imaging of the small bowel is performed in patients with suspected or known CD for many reasons including fear of impaction.[31]

Diagnosing CD on the basis of WCE alone can be difficult as multiple ulcers in the small bowel resembling CD can be seen in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs) [Figure 3].[31] The most commonly used criteria [European Crohn's and Colitis Organization (ECCO)] for an abnormal WCE study is the presence of more than three ulcers in the absence of NSAIDs' use.[31] When this definition was used, WCE had a sensitivity of 77%, specificity of 89%, PPV of 50%, and an NPV of 96% for the diagnosis of suspected CD.[33]

The use of WCE in CD is limited by concerns about persistent capsule retention. This is defined as the presence of the capsule in the GI tract 2 weeks or more after the study.[119] In the general population and in those with suspected CD, the risk of capsule retention is 1-2.5%.[120,121] However, in patients with known CD, the risk is significantly higher at 13%.[121]

Asymptomatic retained capsules can be retrieved by double balloon enteroscopy. Surgery should be considered in patients with symptoms and signs of small bowel obstruction. In one case, the retained capsule passed spontaneously after 2 years. Interestingly, the patient had received anti-TNF agents during that period.[122]

Administration of the patency capsule before WCE may minimize the risk of retention. The patency capsule is made of lactose and barium, and dissolves within 72 hours of entering the GI tract and is of similar size as the endoscopy capsule. Excretion of the intact patency capsule without complications predicts the safe passage of the WCE.[123] Visualization of the entire small bowel with WCE is achieved in less than 85% of the examinations. A study is considered complete when the capsule reaches the cecum during the recording time.[122,124] Attempts to improve the completion of the studies with pro-motility agents have been ineffective.[122,125]

**Small bowel enteroscopy** In CD, the ability to evaluate the entire small bowel can be important as the proximal small bowel may be the only affected area in up to one-third of patients.[120,126]

Traditional endoscopic procedures can evaluate the distal end of the terminal ileum during colonoscopy and the very proximal jejunum with push enteroscopy. In the past, the majority of the small bowel was examined by radiographic contrast studies such as SBFT. Balloon-assisted enteroscopy provides the possibility of direct visualization and sampling of the small bowel. The three main techniques are single balloon enteroscopy, double balloon enteroscopy (DBE), and spiral enteroscopy.

Since its introduction more than 10 years ago, DBE has been the most studied and established technique in deep small bowel enteroscopy.[127] DBE allows intubation (240-360 cm antegrade and 102-140 cm retrograde) deeper than what is possible with push enteroscopy (90-150 cm) or ileocolonoscopy (50-80 cm).[127] Of all patients who undergo DBE for suspected small bowel disorders, CD is found in 5-13%.[127,128] One limitation is that the procedure is unsuccessful in 25% of patients who underwent previous abdominal surgery.[129] Also, it requires special skills, prolonged procedure times, and deeper sedation with the need for general anesthesia in the majority of patients.[127] The risk of complications with diagnostic DBE is around 1%, with pancreatitis being the most common. Endoscopic interventions may lead to a higher risk of perforation and bleeding.[120]

WCE or radiographic studies prior to DBE can direct which route should be taken (oral vs. rectal) to reach the point of interest. The advantage of utilizing DBE over WCE is the ability to obtain tissue samples and apply therapeutic interventions such as dilatation of strictures.[128]

**Spiral enteroscopy** Enteroscopy with the Endo-Ease System (Spirus Medical, Stoughton, MA, USA) uses a spiral-shaped overtube, 118 cm long, with a spiral ridge of 0.55 cm high and 22 cm long and is compatible with enteroscopes less than 9.4 mm in diameter.[120] Spiral enteroscopy takes less time to perform, but the depth of intubation is less than that of DBE. There are limited reports of its use and safety in CD patients. Furthermore, the operative characteristics of spiral enteroscopy are not well defined.

**Chromoendoscopy** Patients with IBD colitis have higher risk of CRC compared to the average population. Traditionally, screening was performed with white light endoscopy and targeted biopsies of visible lesions, as well as 33 interval random biopsies. More recently, the use of pan-colonic chromoendoscopy with targeted biopsies has been shown to improve adenoma detection rate.[130,131]

In chromoendoscopy, dye solutions are applied to the mucosa of the colon, enhancing the recognition of details to uncover the mucosal changes not seen by the optical methods before targeted biopsy and histology[132] [Figure 4]. Methylene blue and indigo carmine are the two most commonly used contrasts in chromoendoscopy. Absorption of methylene blue requires 60 seconds. Stable staining allows for examination of the mucosa for up to 20 minutes. Methylene blue is mainly taken by non-inflamed mucosa as it is poorly absorbed by inflamed mucosa and areas of intraepithelial neoplasia.[132]

A recent meta-analysis showed that pan-colonic chromoendoscopy was significantly better than white light endoscopy in detecting intraepithelial neoplasia in patients with UC. The number needed to treat was 14 to identify one additional patient with dysplasia.[133]

Chromoendoscopy should be avoided in patients with active disease and those with poor bowel preparation due to high rates of false-positive and false-negative findings. Random biopsies should be

taken from areas that are poorly visualized, such as segments with active inflammation or inadequate bowel preparation.[131]

Narrow band imaging (Olympus, Tokyo, Japan) has been considered as an alternative to chromoendoscopy in CRC screening in UC patients. Three studies failed to show the benefit of Narrow band imaging (NBI) over conventional endoscopy.[134,135,136] Performing and interpreting results of chromoendoscopy requires advanced knowledge and experience in this field, and it is not widely available except at some tertiary care centers worldwide.

**Confocal endomicroscopy** Confocal endomicroscopy provides real-time histology evaluation during endoscopy [Figure 5]. It requires the use of intravenous fluorescent agents. The agent distributes within seconds to all compartments of the tissue. It contrasts cellular and subcellular details, connective tissue, and vessel architecture. Neoplastic lesions could be predicted with high accuracy using confocal endomicroscopy. It has a sensitivity of 94.7%, specificity of 98.3%, and an accuracy of 97.8%.[137] The limited number of centers offering this technology restricts the use of confocal microscopy.

## Managing IBD

**Medical advances** *TNF antagonists*: The introduction of anti-TNF therapy for treating IBD was considered a breakthrough in medical management. To date, four TNF antagonists are used for the treatment of CD and UC. IFX (Remicade®) is the first drug of its category to be approved (1998)[138] as it was initially shown to be effective as an induction agent for CD in 1997. Subsequently, multiple studies showed superior effect of this drug in treating fistulizing and non-fistulizing CD[139,140,141,142,143] and severely active UC[144,145] in large multicenter randomized placebo-controlled settings. IFX is given as an intravenous infusion of 5 mg/kg at weeks 0, 2, and 6 for induction, followed by 5-10 mg/kg every 8 weeks (often decreased to every 6 weeks) for maintenance. Further, the use of IFX has extended to the treatment of ankylosing spondylitis, rheumatoid arthritis (RA), plaque psoriasis, and psoriatic arthritis.[146,147,148] It was estimated in 2007 that 1 million patients worldwide were being treated with IFX.[149] IFX remains fairly expensive, especially to patients who reside in countries where health insurance is not available, and requires the presence of certain health resources for administration, including infusion centers, well-trained nurses, and physicians familiar with managing adverse events such as infusion reactions and opportunistic infections. These limiting factors stand between patients who are in need of treatment and providing IFX in many parts of the world. ADA (Humira®) is a humanized IgG1 monoclonal antibody (mAb) that irreversibly binds with high affinity and specificity to soluble TNF-α. ADA was first approved for the treatment of CD in 2008 after its efficacy as an induction agent for patients with moderate to severely active biologic-naïve CD was found.[150] ADA has since been proven effective as a maintenance agent in treating biologic-naïve and biologic-experienced CD[151,152,153] and, more recently, as an induction/maintenance agent for UC.[154] In comparison to IFX, ADA is self-administered subcutaneously (SC) but given more frequently to maintain remission (every 2 weeks). ADA, however, is similar to IFX in terms of high cost and widespread use as it is approved in 83 countries and prescribed to almost 500,000 patients with RA worldwide.[155] Certolizumab Pegol (CTZ) (Simzia®) is the third anti-TNF agent to be approved for the treatment of IBD, but its use is limited to inducing and maintaining remission in CD.[156,157,158,159,160,161] CTZ is a humanized antibody fragment (Fab) that is administered SC, and possesses advantages over other TNF antagonists, such as having a long half-life, not crossing the placenta, and not being excreted into breast milk because it is linked to a polyethylene glycol (PEG) moiety and is therefore ideal for pregnant females with IBD requiring anti-TNF therapy.[162,163] CTZ is FDA approved and is only otherwise approved in Switzerland mainly due to cost reasons, and its use has therefore been limited to patients with refractory disease mostly under compassionate circumstances. The newest anti-TNF agent to have emerged recently is Golimumab (GOL) (Symponi®), which is a fully human mAb directed against TNF-α and is given as an SC injection.[164] Studies on GOL are ongoing, but reports to date are encouraging and suggest that it is indeed effective in inducing clinical response remission in patients with moderate to severe UC[165] and is expected to be the next agent of this class to be approved for this indication. Critically, the exact duration of effect provided by these agents remains unclear. Additionally, there has also been some controversy surrounding the concept of "generalizability" given how RCTs involving TNF antagonists mostly exclude initial non-responders.

*Leukocyte trafficking inhibitors*: The concept of interfering with leukocyte trafficking to areas of inflammation has evolved over the past decade into the development of therapeutic drugs for the treatment of multiple sclerosis (MS) and IBD.[166] Natalizumab (NTZ) (Tesabri®), a humanized IG4 mAb that inhibits leukocyte adhesion through antagonizing α4 integrin, was first proven to be an effective agent for the treatment of relapsing MS.[167,168] Subsequently, NTZ was studied in multiple large-scale multicenter RCTs in CD and showed effectiveness in the induction and maintenance of remission in patients with active CD.[169,170,171] The reporting of several cases of progressive multifocal leuko-encephalopathy (PML), however, resulted in temporary withdrawal of NTZ from the market by the FDA.[172,173,174,175,176] After extensive investigations, NTZ was re-approved for the treatment of MS and refractory CD, and is currently only FDA approved and available through limited access in a few specialized IBD centers worldwide.[177] Vedolizumab (VDZ; previously known as MLN002) is a selective inhibitor of the integrin α4β7, a molecule with a central role in the process of leukocyte trafficking.[178] VDZ is believed to exclusively target leukocyte adhesion in the gut and is therefore "gut specific."[179,180] Many phase I and II clinical trials of VDZ in IBD have proven the drug to be effective as an induction and maintenance agent for both UC and CD.[181,182,183,184] Furthermore, encouraging results of phase III RCTs that focused on the effect of VDZ in treating IBD (UC and CD) have recently been released.[185,186] This category of drugs is considered by some experts to be revolutionary in the treatment of IBD. The chilling effect caused by the reporting of PML with NTZ has and will likely continue to slow down the development of leukocyte (LKC) trafficking inhibitors. Historically, rare side effects have been reported with medications thought to be safe after a large number of patients have been exposed to them in clinical practice or as part of long-term extension studies, which will be a cause of concern with this category of drugs.

*Interleukin (IL)-12/23 inhibitor*: Ustekinumab (UKB) (Stelara®) is a fully human IgG1 mAb that inhibits IL-12/23 through targeting their shared p40 subunit. UKB is effective in the treatment of psoriasis[187,188] and was shown in two large multicenter RCTs to be an effective agent for the induction and maintenance of remission for patients with moderate to severely active CD refractory to anti-TNF therapy.[189,190] UKB, however, is not approved yet for this indication, but is available through compassionate measures in some centers.

*Probiotics*: Normal colonic bacterial flora plays an important role in regulating innate and adaptive immune responses to foreign pathogens. Accordingly, any alteration in the normal flora is a breach in this highly coordinated system and can ultimately lead to the development of diseases such as IBD.[191] Theoretically, replacing the bacterial flora that inhabits the bowel of IBD patients can help in regaining normal symbiosis. This theory was behind the introduction of probiotics as a therapeutic option for patients with IBD. Probiotics have been well studied in pouchitis and shown to be effective in inducing and maintaining remission as well as the prevention of pouchitis.[192,193,194,195,196,197,198,199] Additionally, the use of probiotics has recently been found to be an effective strategy to treat cases of mild to moderately active UC[200,201,202] through inducing and maintaining remission, as well as of CD through maintaining remission.[203] The main limiting factor to the use of probiotics in IBD remains their cost.

## Therapeutic drug monitoring

**TPMT testing and 6-mercaptopurine metabolites** Thiopurines [Azathioprine (AZA) and 6-mercaptopurine (6MP)] are the commonly used immunosuppressants that are proven effective for the treatment of IBD and have been used for over five decades. The use of AZA and 6MP is limited by the development of adverse events or lack of response leading to failure of therapy. These limitations can be counteracted by the following pharmacological strategies.

Multiple studies have shown that thiopurine methy ltransferase (TPMT), the key enzyme in AZA metabolism [Figure 6], plays a significant role in mediating drug toxicity.[204] TPMT enzyme activity varies among individuals. About 90% of Caucasian populations have normal activity, with 10% having intermediate activity. Approximately 1 in 300 people has negligible TPMT activity, which correlates with a significant risk of fatal bone marrow suppression.[205] Previous studies have shown strong concordance between TPMT genotype and phenotype, i.e. enzyme activity, ranging from 77 to 99%.[206] However, multiple reported cases demonstrated severe myelosuppression in patients who are wild-type or

heterozygous carriers for the common TPMT variant alleles,[207] leading to the argument that TPMT activity (phenotype) might be a safer screening tool compared to genotype testing for the prevention of severe myelosuppression. TMPT testing prior to initiating thiopurine therapy is now considered the standard of care. It is still unclear if using TPMT as the standard of care is economically beneficial and, therefore, has not been widely implemented. Surveys that characterize how much the TPMT use has changed the practice of IBD treating physicians and the overall outcome of patients are lacking.

AZA is an effective maintenance and steroid-sparing therapy for IBD. However, the mean dose response period is approximately 17 weeks due to the slow accumulation of 6-thioguanine (6-TGN) (active metabolite)[208] and there is a significant correlation between 6-TGN levels and clinical response. Dubinsky *et al*. reported an OR of 5.0 (95% CI 2.6-9.7, $P < 0.001$) for therapeutic response when 6-TGN levels were above 235 pmol/$10e^8$ red blood cells (RBCs).[209] Likewise, in a study by Cuffari *et al*., 6-TGN level of 292 pmol/$10e^8$ RBCs was associated with a PPV of 85.7% for clinical response.[210] However, close clinical monitoring is required upon dose escalation due to an inherent preferential production of 6-methyl mercaptopurine (6-MMP).[211] Another approach for increasing 6-TGN levels is by adding either allopurinol (XO inhibitor) or a 5-aminosalicylic acid (5-ASA) agent, which manipulates the metabolic pathway toward the desired effect and, therefore, achieves adequate clinical response without the potential side effects secondary to 6-MMP.[212,213,214,215,216] The practice of using 6-mercaptopurine (6-MP) metabolites to guide thiopurine dosing is not widely acceptable. This is mainly due to the paucity of studies that support their benefit and the reservations exhibited by many physicians toward the safety of this practice.

**Monitoring the response to biologics** TNF antagonists are effective induction and maintenance therapies for CD and UC.[142,217,218] IFX and ADA have shown clear benefits over conventional therapies for maintaining clinical remission, and decreasing the rates of hospitalization, steroid requirements, and the need for surgery among IBD patients.[151,219,220,221,222] However, initial induction therapy fails in 30% of patients (primary non-response), with 50% of the responders losing response overtime (secondary non-response).[223] The current approach for managing secondary non-responders is by increasing the dose or shortening the treatment interval to theoretically maintain adequate serum drug concentration.[224,225,226,227] The ability to measure serum drug levels and anti-IFX antibodies (ATI), otherwise known as human anti-chimeric antibodies (HACA), further enhances the outcome of this approach.

**Infliximab drug levels and HACA detection** One of the major factors that adversely affect the pharmacokinetics of TNF antagonists is the formation of anti-drug antibodies. These antibodies compromise the biological activity of anti-TNF therapy by accelerating the drug clearance through the formation of immune complex by the reticuloendothelial system and/or by impairing its binding to TNF.[228,229] The presence of ATI leads to subtherapeutic trough levels, and accordingly, higher rates of treatment failure[225,230,231] as it is associated with 34% shorter half-life and 2.7-fold increased clearance.[232] There are two assays available that can assess drug and anti-drug antibody concentrations. The commonly used method is the enzyme-linked immunosorbent assay (ELISA), but this assay is limited by the inability to measure antibody in the presence of circulating drug.[224,230] The second method is the radioimmunoassay (RIA), which is more sensitive and specific than ELISA. However, there is insufficient information regarding the performance of RIA in the evaluation of drug anti-drug antibody concentration in patients with IBD.[231,233] A newer liquid-phase mobility assay [homogenous mobility shift assay (HMSA) using size-exclusion high-performance liquid chromatography (SE-HPLC)] has been developed for the measurement of drug concentration and anti-drug levels without the limitations of the previously described methods (ELISA, RIA). This assay is able to detect drug concentration and antibody in the same serum sample.[234]

**ADA drug levels and HAHA detection** As previously described, ADA is an effective agent for inducing and maintaining remission in IBD.[150,220,235] Elevated ADA trough levels have been linked to higher rates of clinical remission. In the CLinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC) I and II studies, the mean concentration level of ADA was higher among patients who achieved clinical remission compared to those who did not.[236] However, other studies have shown no significant correlation between ADA trough concentration and the maintenance effect of ADA, as seen in a study by Karmiris *et al*. where there was no relationship between ADA trough concentration or anti-drug antibodies with clinical outcome among 191 patients treated with

ADA.[237] Although theoretically ADA is fully humanized, human anti-human antibodies (HAHA) can still develop and are thought to be associated with failure of therapy. HAHA have been measured in clinical trials, but are not available commercially. Studies to prove that measuring the drug levels and antibodies increase the clinical response and remission rates are in need.

**Endoscopic advances** Strictures are a common complication of CD that can lead to recurrent hospitalizations and debilitating disease course. They can occur in any part of the GI tract, but usually appear at anastomotic sites (post-surgery), terminal ileum, and rectum.[238] Clinically significant stricture is defined as persistent luminal narrowing with prestenotic dilatation associated with obstructive symptoms. Strictures can be predominantly inflammatory in nature, and this type tends to respond to modulation of therapy or escalation in medical treatment, whereas fibrostenotic strictures do not typically respond to medical treatment and surgical resection is the only definitive treatment. This eventually can lead to chronic diarrhea, and multiple resections ultimately lead to short bowel syndrome. Therefore, more conservative approaches including endoscopic balloon dilatation (EBD) as well as endoscopic stenting should be considered.

*Endoscopic balloon dilatation*: The literature regarding the role of EBD is mainly limited to short-term non-controlled observational studies involving small numbers of patients. Therefore, the long-term efficacy and safety of EBD is not yet well defined. Couckuyt *et al*. reported a procedure success rate of 90% in a prospective follow-up study of 55 CD patients with ileo-colonic stricture who underwent 78 dilatations.[239] The symptom-free rate was 62%, lasting up to 11 months. However, serious complications such as perforation occurred in 11% (8% of procedures). This high rate of complications might be related to the fact that the initial balloon size used was 18 mm and fluoroscopy was not utilized in all procedures. Recently, larger studies with longer follow-up periods reported similar high initial technical success rate with less complications but lower long-term clinical success rate likely explained by a longer follow-up period. One study included 138 patients who underwent 237 dilatations for a clinically obstructive stricture; an immediate success rate was achieved in 97% with a 5% serious complication rate.[240] After a median follow-up of 5.8 years, recurrent obstructive symptoms led to a new dilatation in 46% or surgery in 24%. Furthermore, a large retrospective single cohort study with 776 dilatations involving 178 patients with CD had a technical success rate of 89%.[241] At 1, 3, and 5 years, no further intervention or one additional dilatation at the most occurred in 80%, 57%, and 52% patients, respectively. The overall complication per procedure rate was 5.3%, including bowel perforation (1.4%), major bleeding (1%), minor bleeding (1.3%), and abdominal pain or fever (1.5%).

A meta-analysis of 13 earlier studies conducted between 1990 and 2007 included a total number of 347 CD patients and 695 dilation procedures. The technical success rate was 86%, long-term clinical success rate was 58%, and the rate of major complications was 2%.[242] In a multivariate analysis, a stricture length ≤ 4 cm was associated with a surgery-free outcome. In addition, anastomotic strictures were associated with better long-term outcomes than *de novo* strictures in a recent long-term retrospective study.[243] Furthermore, smoking has been found to double the risk of recurrent stricture formation, requiring a new intervention after first dilatation.[244] However, neither active disease at the time of the dilatation nor medical therapy afterward predicted recurrent dilatation or surgery.[240] EBD, when performed in selected patients with Crohn's related fibrostenotic stricture, is relatively safe with positive long-term effect and is considered a useful alternative to surgery when available. However, the high risk generally associated with EBD and the need for special training is the main limitation to its use.

*Endoscopic stenting*: Another endoscopic approach available to treat cases of CD with refractory fibrostenotic stricture involves the placement of a temporary self-expandable metal stent (SEMS) through the endoscope.[245] Although it sounds feasible, the experience with this procedure is very limited and early results have raised serious safety concerns such as perforation, fistula formation, stent migration, and difficult stent extraction.[246,247] However, the use of stents with an anti-migratory design[248] and biodegradable stents[249] showed encouraging results, but their long-term efficacy and safety requires further studies.

**Surgical advances for UC** *Total colectomy with end ileostomy*: One of the surgical options to be offered to UC patients in an elective setting is total proctocolectomy with end ileostomy. An end ileostomy should be considered for patients who are at risk for pouch failure, such as patients with impaired sphincter

function, advanced age, previous ano-perineal disease,[250] or for patients who opted not to have a pouch. A recent analysis using The American College of Surgeons National Quality Improvement Project (ACS-NSQIP) database which included 1077 UC patients who underwent colectomy showed that laparoscopy was associated with lower morbidity (complication rate 21 vs. 32%, $P < 0.001$) and mortality rates (0.2 vs. 1.7%, $P = 0.046$) when compared to open surgical approaches.[251] In this national study, 28% of the procedures were performed laparoscopically, with an 8.5% annual increase of utilizing laparoscopic colectomy in UC patients.[251] Minimally invasive laparoscopic total proctocolectomy has also been reported as a safe alterative to the open approach.[252,253]

*Restorative proctocolectomy with IPAA*: Restorative proctocolectomy with an IPAA, originally described in 1978 by Parks, is currently considered the standard surgical treatment for patients with UC in certain elective settings [Figure 7].[254] The purpose of the operation is to remove all the colonic mucosa to eliminate cancer risk, and preserve continence by creating a pouch that is anastomosed to the anus [Figure 1]. IPAA is a technically demanding procedure with excellent functional outcomes and improved quality of life;[255] however, it is not without complications. The incidence of early complications is 42%, with a low mortality rate. Early complications include pouch–anal anastomotic leak, bowel obstruction, and wound infections.[256] Late complications occur in 36% of cases, which include pouchitis, bowel obstruction, pouch-associated fistula, intra-abdominal infections, infertility, stricture formation at the pouch–anal anastomosis, and cuffitis.[256,257,258,259] Pouchitis is the most common late complication after IPAA, and its incidence varies between 16 and 48%. Laparoscopic IPAA can be performed safely with better short-term outcomes, including shorter time to regular diet, less narcotic use, and shorter length of stay, with comparable complication rates to the open approach.[260] These operations require skilled and experienced surgeons with a dedication toward performing a large volume of colorectal surgeries, which is mainly available in specialized tertiary care centers. The long-term outcome of this intervention is still unclear. Further, the high rate of complications and disease recurrence with IPAA argues that the overall quality of life (QOL) provided to these patients is poor and underscores the need for better surgical approaches. QOL studies for this purpose are therefore needed.

**Surgical advances for CD** *Laparoscopic bowel resection*: Despite the advancement in the medical management of CD, 70–90% of the patients undergo surgery during the course of their disease.[261] Surgery is indicated for complications secondary to CD, including perforation, failure of medical management, small bowel obstruction, fistulas, or malignancy. Surgery can be performed as open or laparoscopic. Laparoscopic ileocecal resection is feasible and safe with a lower 5-year risk of small bowel obstruction compared to open approach (5% vs. 9%, $P = 0.25$), but they have similar risk for recurrence.[262] Patients who have had laparoscopic resection had faster recovery of pulmonary function, fewer complications, and shorter length of stay compared to the selected patients opting for conventional open approach who underwent ileocecal resection.[263,264]

## Cost-effectiveness and resource allocation

Cost remains a huge challenge for both patients with IBD and their treating physicians.[265] The financial burden of IBD extends beyond the cost of therapy to include hospitalizations, diagnostic work-up, surgery, and days lost from work.[266] In the era of biologic therapy, health care budgets often question whether or not such therapies provide a cost-effective approach when compared to standard medical care. Multiple cost-effectiveness studies have been performed specifically directed toward biologic therapies.[267] A retrospective audit of all cases of CD treated in seven centers in the UK showed that IFX treatment is potentially cost-effective as a result of less hospitalizations, examinations under anesthesia, and diagnostic procedures over a 6-month period following initiation of treatment.[268] Similarly, a cost-utility analysis of data from the CHARM and the CLASSIC I studies showed that ADA is cost-effective as a maintenance agent when compared to conventional non-biologic therapy in cases of moderate to severely active CD.[269] No data exists on the cost-effectiveness of newer agents such as leukocyte trafficking inhibitors. As such, optimizing the use of biologic therapy is necessary to preserve the economic resources and ensure proper resource allocation. This is provided through prescribing such therapy in the proper setting with systematically scheduled therapy combined with close monitoring for loss of effect or development of adverse events that would prompt discontinuation of the drug. A recent analysis has also confirmed that a test-based approach for monitoring anti-TNF therapy is more cost-effective when compared to empirical dose escalation in patients with CD who lose response.[270] Collectively, it is obvious that the cost

inferred by the newly developed therapies for IBD is a key limiting factor and whether these proposed cost savings would be maintained over longer periods of follow-up.

## CONCLUSION

Management of IBD is rapidly evolving with the design of more useful evaluative tools and the ever-expanding development of effective drug therapies. Even though there are many advances in IBD management that have made their way into clinical practice in Europe and North America, there is still limited use of these tools in many parts of the world, including the Middle East, South Asia, South America, Far East, and most parts of Africa, due to their high cost, limited data, and dependence on experience. This has to be kept in mind when defining standard of care. Furthermore, sufficient expertise, medical training, cost, and staffing plus availability of a medical database and/or registry and electronic health record among many other factors define availability. Less-invasive, safe, and relatively inexpensive evaluative strategies such as noninvasive markers of inflammation and small bowel US have potential benefits. Therapies that are clearly beneficial, safe, and cost-effective are yet to be identified.

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## Figures and Tables

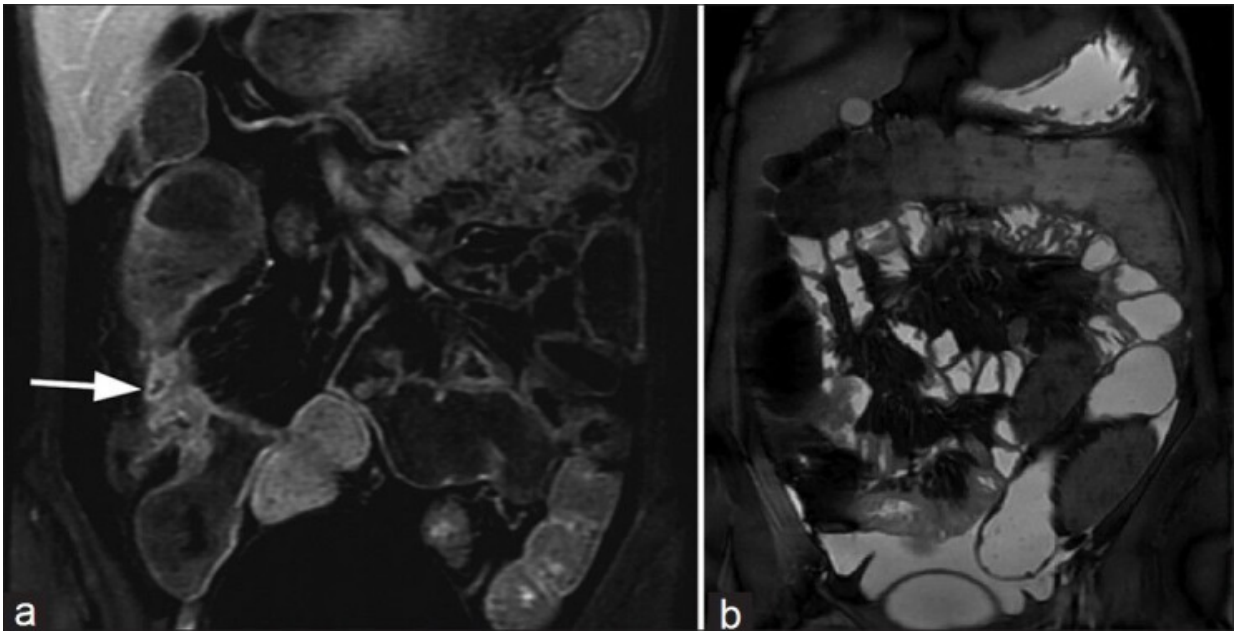
**Table 1**

| Characteristic modality | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| SBFT/SBE | 40-100 | 95.8-100 | 89-100 | 50-80.2 |
| WCE | 77-92 | 89-100 | 50-100 | 92-96 |
| US | 76-92 | 95-98 | 92-98 | 58-92 |
| CT imaging | 77-88 | 90-100 | 88-100 | 69-90 |
| MR imaging | 88-98 | 78-100 | 83-100 | 66-90 |

PPV: Positive predictive value, NPV: Negative predictive value SBFT: Small bowel follow through, SBE: Small bowel follow, WCE: Wireless capsule endoscopy, MR: magnetic resonance, US: Ultrasonography, CT: Computed tomography

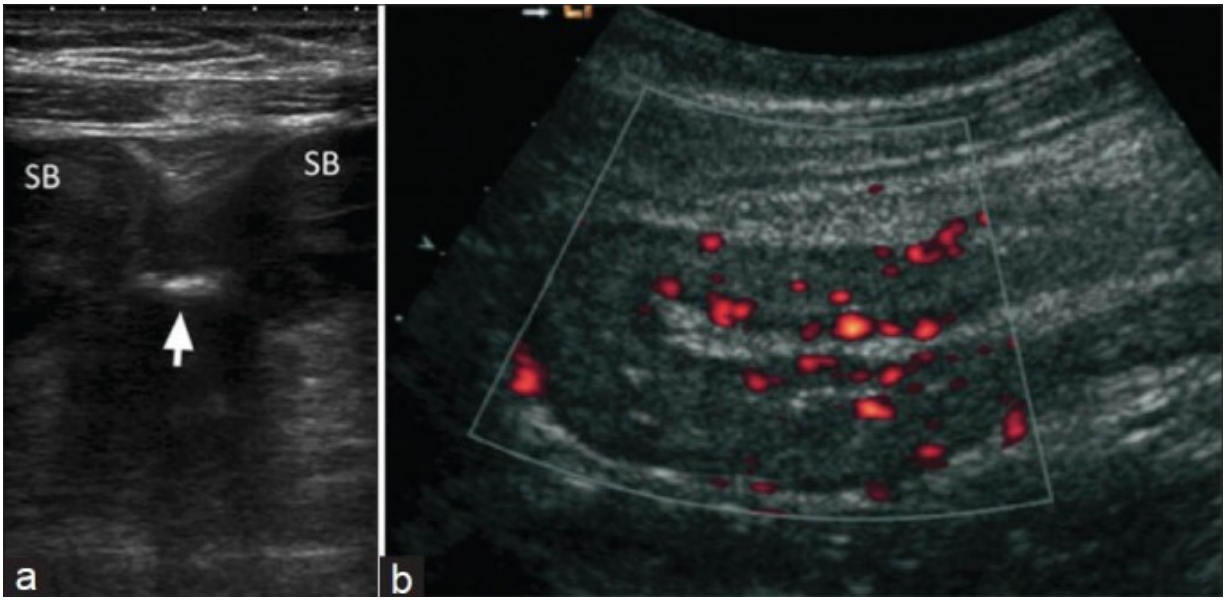
Operator characteristics of different diagnostic modalities used for inflammatory bowel disease

## Figure 1



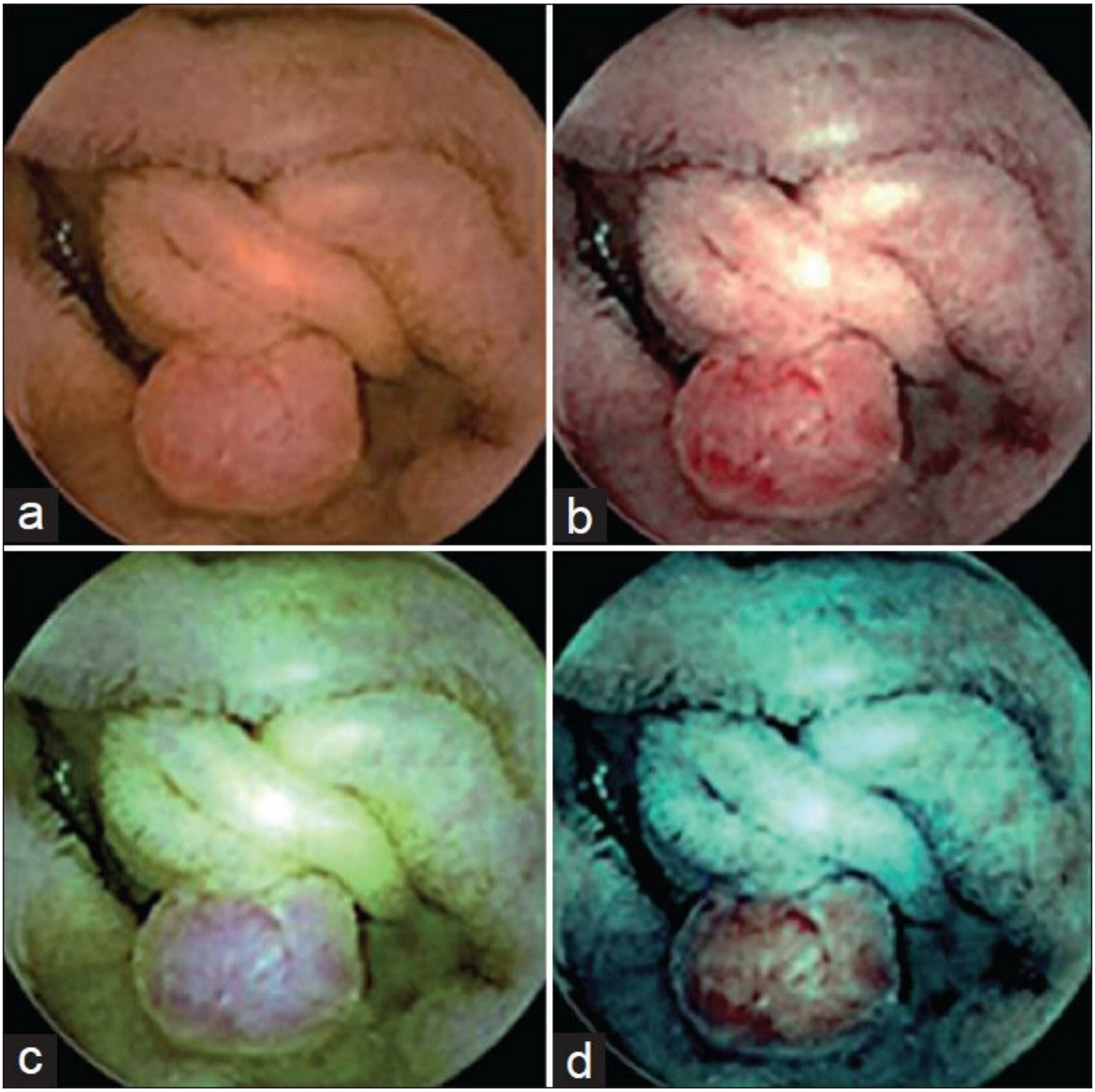

(a) Coronal gadolinium-based contrast material–enhanced fat-suppressed T1-weighted gradient-echo MR image shows luminal narrowing, mural thickening, and mildly increased vascularity of the terminal ileum (arrow). (Reproduced with permission from Leyendecker *et al.*, MR enterography in the management of patients with Crohn disease. Radiographics, 2009. 29 (6): p. 1827-46.) (b) MRE demonstrating thickening and enhancement of the distal ileum associated with mesenteric fat creeping and engorgement of vasa recta in a 23-year-old female known to have Crohn's disease for 4 years

## Figure 2



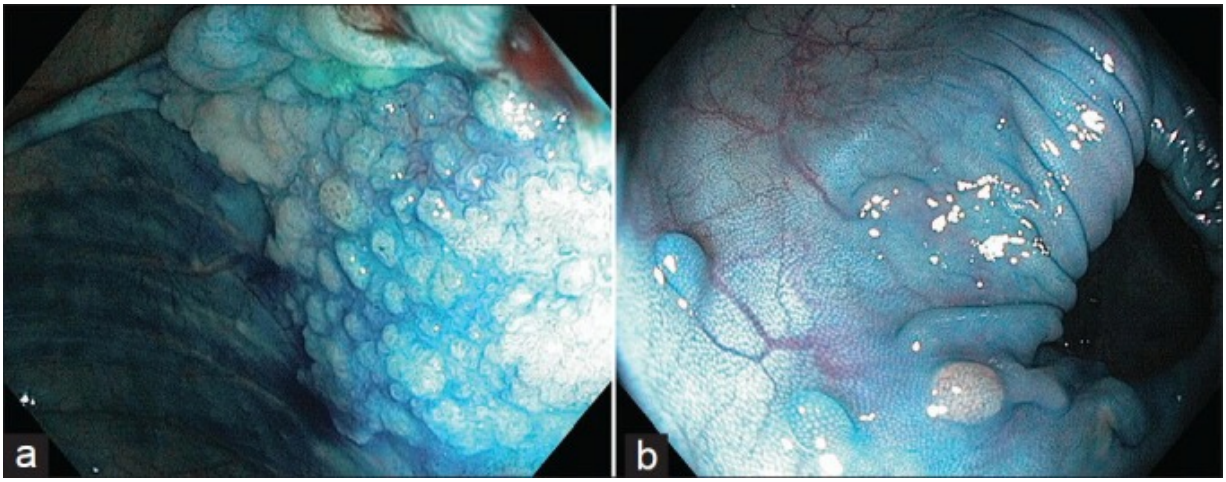

(a) Small bowel ultrasonographic images showing a lineal communication between two thickened small bowel loops which contains air (arrow), corresponding to an entero-enteric fistula. (b) Small bowel ultrasonographic images showing bowel wall thickening with moderate positive vascularity on Doppler. Surrounding peri-enteric fat has an increased echogenicity because of inflammatory changes. (Reproduced with permission from Panes *et al.*, Systematic review: The use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther, 2011. 34 (2): p. 125-45)

## Figure 3



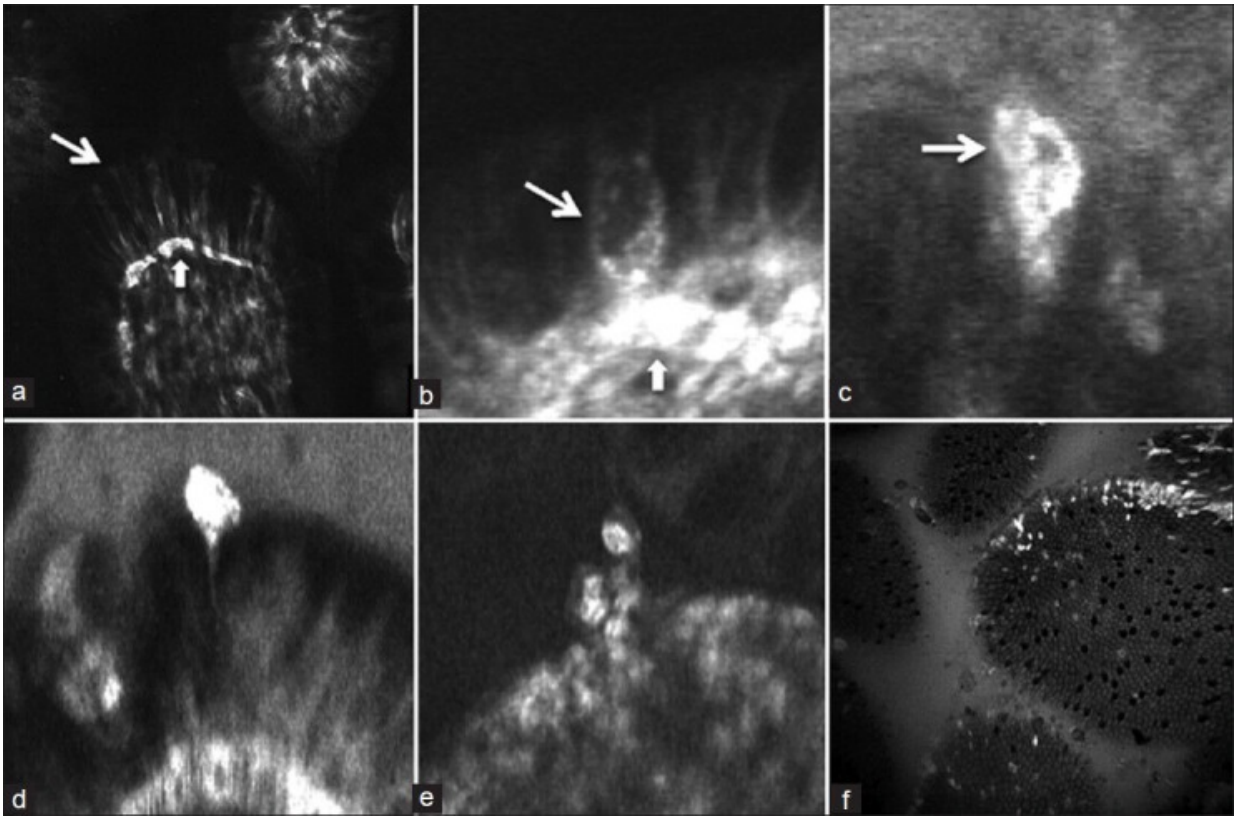

FICE images captured by video capsule endoscopy seen with (a) conventional imaging, (b) FICE setting 1 (red 595 nm; green 540 nm; blue 535 nm), (c) FICE setting 2 (red 420 nm; green 520 nm; blue 530 nm), and (d) FICE setting 3 (red 595 nm; green 570 nm; blue 415 nm) (FICE: Fujinon Intelligent Color Enhancement). (Permission obtained from Thieme Publishers©; reproduced with permission from Fisher LR and Hasler WL, New vision in video capsule endoscopy: Current status and future directions. Nat Rev Gastroenterol Hepatol, 2012. 9 (7): p. 392-405)

## Figure 4



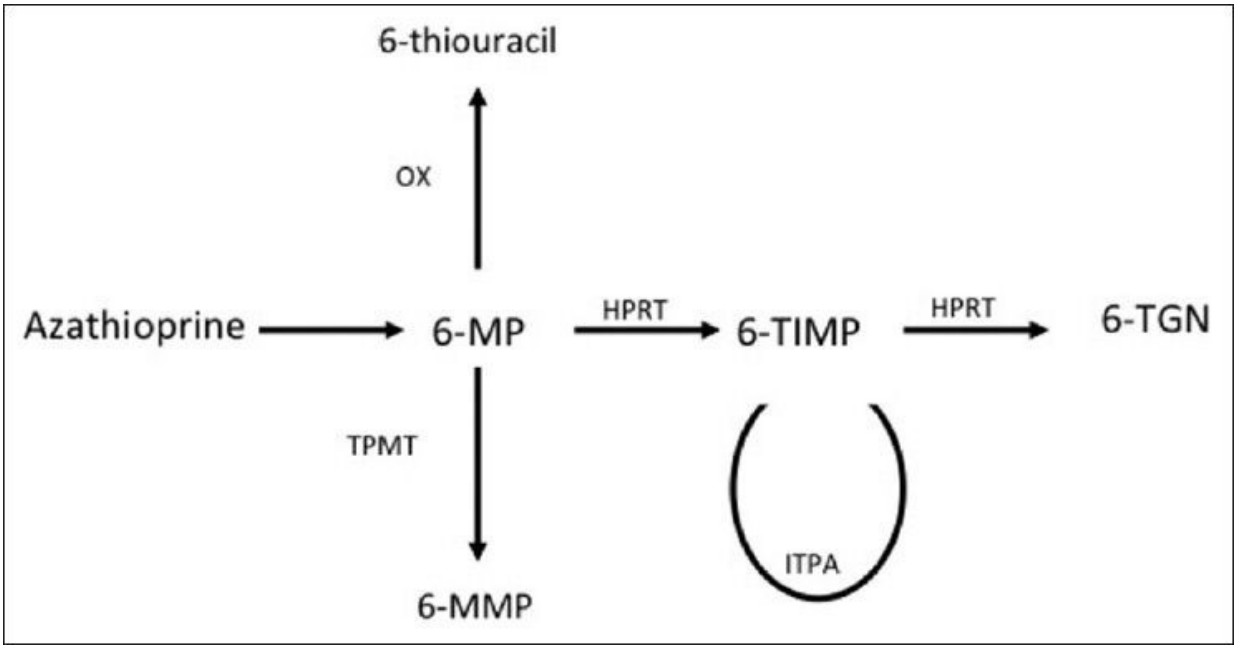

Chromoendoscopic images of (a) a dysplasia associated lesion or mass, (b) multiple pseudo polyps in ulcerative colitis

## Figure 5



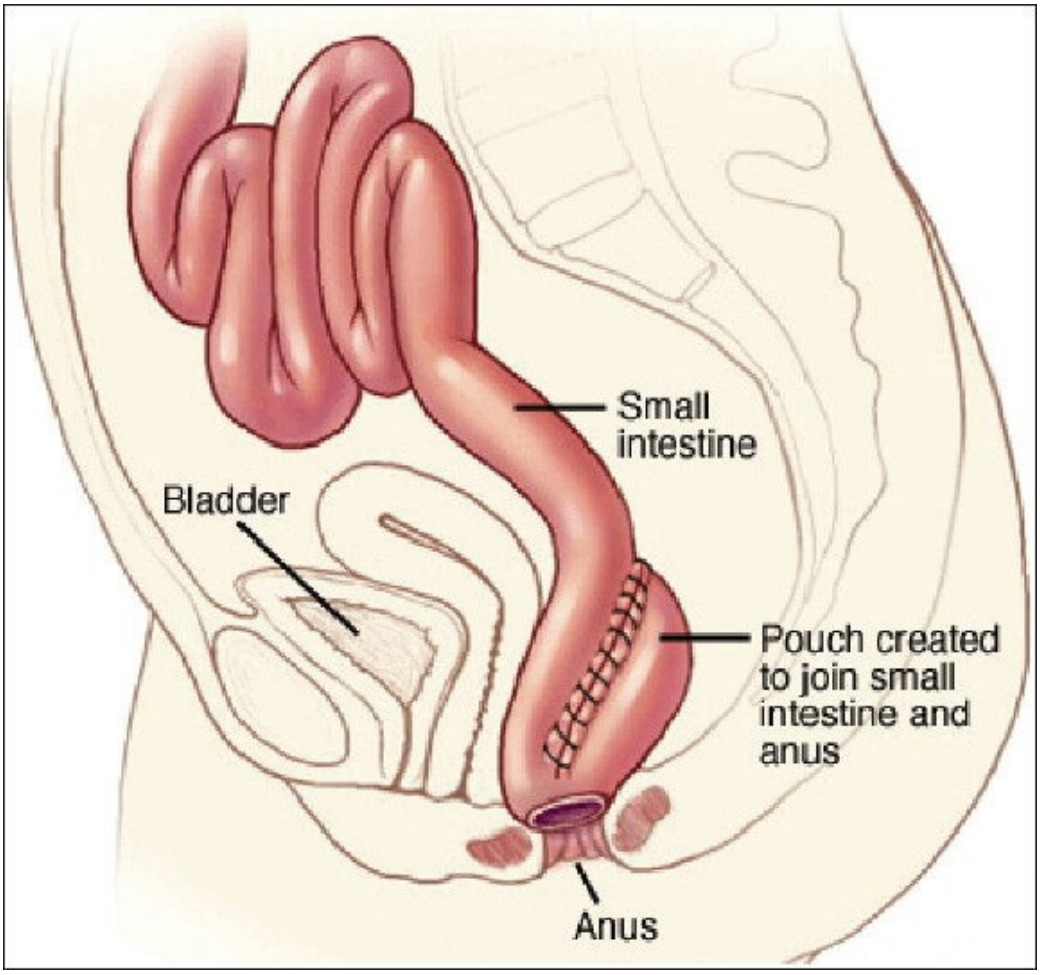

Confocal endomicroscopic imaging of epithelial cell shedding in the terminal ileum. (Reproduced with permission from Kiesslich *et al.*, Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. Gut, 2012. 61 (8): p. 1146-53)

## Figure 6




The metabolic pathway of thiopurines

## Figure 7




An illustration of a surgically constructed ileal pouch

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