



2016 Inflammatory Bowel Disease: Global view

How to predict clinical relapse in inflammatory bowel disease patients

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Abstract

Inflammatory bowel diseases have a natural course characterized by alternating periods of remission and relapse. Disease flares occur in a random way and are currently unpredictable for the most part. Predictors of benign or unfavourable clinical course are required to facilitate treatment decisions and to avoid overtreatment. The present article provides a literature review of the current evidence on the main clinical, genetic, endoscopic, histologic, serologic and fecal markers to predict aggressiveness of inflammatory bowel disease and discuss their prognostic role, both in Crohn's disease and ulcerative colitis. No single marker seems to be reliable alone as a flare predictor, even in light of promising evidence regarding the role of fecal markers, in particular fecal calprotectin, which has reported good results recently. In order to improve our daily clinical practice, validated prognostic scores should be elaborated, integrating clinical and biological markers of prognosis. Finally, we propose an algorithm considering clinical history and biological markers to intercept patients with high risk of clinical relapse.

Key words: Crohn's disease; Ulcerative colitis; Clinical relapse; Clinical predictors; Fecal calprotectin

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Core tip: Natural course of inflammatory bowel diseases (IBD) is mostly unpredictable so far. Predictors of benign or unfavourable clinical course are required to facilitate treatment strategies. Our aim is to review current evidence on the main clinical and biological markers to predict the aggressiveness of IBD and to discuss their prognostic role. No single marker

is reliable as a flare predictor but a combination of clinical and biological indicators better serves our requirements; we propose an algorithm applicable in our daily practice, arising from a combination of clinical history and biological markers.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are characterized by a relapsing and remitting course. Aim of therapy is both to induce and maintain an enduring remission and to avoid disease progression. Disease flares occur in a random way and are mostly unpredictable, and persistent inflammatory activity negatively affects the patient's physical and psychological well-being, social performance and working capacity.

Despite an effective medical therapy that could guarantee clinic remission, a degree of subclinical inflammation may persist within the mucosa of the gut, contributing to a risk of "symptomatic" relapse, which occurs when the inflammatory process reaches a critical intensity^[1]. Identifying objective markers able to reveal such subclinical inflammation could represent an important advance in clinical practice, allowing the gastroenterologist to select patients and plan a tailored treatment. Clinical, genetic, endoscopic, histologic, serologic and fecal markers have been studied over many years, but we have not yet found an ideal tool to be used for prognostic purposes. Several authors have focused their efforts on this matter, but studies show conflicting and variable results.

CLINICAL PREDICTORS

Clinical predictors of IBD recurrence have probably been the most widely studied and have been received recently^[2-4] (Table 1).

Brignola *et al.*^[5] first found in a cohort of Crohn's disease (CD) patients, that when comparing the clinical features of patients relapsing within 18 mo with those of non-relapsing patients in persistent remission, a shorter period of remission before relapse seemed to have prognostic relevance.

This observation was confirmed by GETAID group^[6] a few years later in a retrospective study; the authors, considering 178 quiescent CD patients not induced by surgery (CDAI < 150) within a median follow up of 23 mo, found that a young age (< 25 years) whether at first symptoms, at diagnosis or at consultation, was related to a high risk of clinical relapse. Furthermore,

Table 1 Clinical and environmental predictors of relapse in inflammatory bowel diseases patients

	CD	UC
Clinical factors		
Age	Young age at diagnosis ^[6-8,10] → <i>Disabling chronic disease</i>	Young age at diagnosis ^[11,14,15] → <i>Rate of relapse</i>
Sex		Female ^[11,14] → <i>Rate of relapse</i>
Disease location	Perianal disease ^[7,9] → <i>Poor outcome</i> Terminal ileal location ^[8,9] → <i>Predictor of stricturing/penetrating disease; risk of surgical resection</i> Proximal small bowel/upper gastro-intestinal tract ^[10,11] → <i>risk of relapse; risk of surgical resection</i> Colonic disease ^[6] → <i>risk of develop perianal disease</i>	Extensive colitis ^[8,14,16] → <i>risk of colectomy, CRC, mortality</i>
No. prior relapses	Short period of remission before relapse ^[5,6] → <i>poor prognosis</i>	Greater number of prior relapse → <i>shorter time to relapse</i>
EIM	NS ^[12]	NS ^[12]
Environmental factors		
Smoke	Disease severity ^[19,20]	↓ disease severity ^[21]
Appendectomy	Risk of surgical resection ^[24]	↓ risk of colectomy ^[22,26]
Drugs		
NSAIDs/ COX-2 selective	Contrasting evidences ^[28]	Contrasting evidences ^[28]
OCPs	Risk of relapse ^[20]	NS ^[15]
HRT	↓ disease severity ^[29]	↓ disease severity ^[29]
Antibiotics	↓ risk of relapse ^[30]	NS ^[30]
Stress	Risk of relapse ^[32]	Risk of relapse ^[31]

CD: Crohn's disease; UC: Ulcerative colitis; CRC: Colon-rectal cancer; EIM: Extraintestinal manifestation; NS: No significant; NSAIDs: Non-steroidal anti inflammatory drugs; COX-2: Cyclooxygenase-2; OCPs: Oral contraceptive pills; HRT: Hormone replacement therapy.

a short interval since the previous relapse (< 6 mo) and colonic involvement were associated with a poor prognosis. In this study neither the presence of anoperineal lesions nor a history previous intestinal resection was found to be of prognostic value.

Population-based studies with a fixed 5-year or 10-year study period after diagnosis of IBD have confirmed that young age at onset, but also disease location, are associated most strikingly with disease course, both in CD and in ulcerative colitis (UC). As regards CD, some authors assumed that the need for steroid treatment at the first presentation, together with perianal disease and young age at onset could be factors associated with a poor outcome^[7]. In particular, patients younger than 40 years at diagnosis have been proven to experience a debilitating chronic disease (OR = 2.1, 95%CI: 1.3-3.6)^[7]. Terminal ileal location seems to be a strong predictor of stricturing and internal penetrating behaviour (including perianal fistulas and abscesses) and an increased rate of surgery^[8,9].

Proximal small bowel and upper gastrointestinal tract location are associated with increased risk of recurrence and surgery^[10,11]. As regards extraintestinal manifestations, the presence of erythema nodosum and pyoderma gangrenosum at diagnosis or later have been demonstrated to be unable to predict a more severe CD course^[12].

Looking at the same issue but from a reverse perspective, we could define a “non severe” evolution of the disease as a clinically inactive disease for longer than 12 years with less than one intestinal resection without a permanent stoma. The factors independently associated with a “non-severe” 15 years clinical course were non smoking status, rectal sparing, high educational levels, older age and longer disease duration^[13].

In UC, young age at diagnosis and female gender are associated with more frequent relapses^[11,14]. In a study by Bitton *et al.*^[15], UC patients with a younger age at onset, particularly the age group between 20-30 years, had a shorter time to relapse ($P = 0.003$). A greater number of prior flares was associated with a shorter time to relapse in women but not in men. Extensive colitis at presentation consistently appears as an independent predictor of colectomy within 10 years after diagnosis. Furthermore, extensive colitis is associated with increased risk of colon cancer as well as a slight increase in mortality^[14,16,17]. A high level of systemic clinical symptoms at presentation (fever, weight loss) was linked to a trend toward infrequent relapses and chronic disease, but a higher risk of colectomy^[16].

ENVIRONMENTAL FACTORS

It has been argued that environmental factors might play a role in precipitating clinical relapse, with particular reference to some medications and lifestyle factors^[18] (Table 1). Smoking is considered one of the stronger predictors of disease course: it globally increases disease severity in CD^[19,20], while an inverse association has been surprisingly documented for UC^[21]. As with smoking, appendectomy is another environmental factor that seems to have opposite effects based on the disease. It is still debated whether appendectomy can increase the risk of CD onset^[22,23]. Appendectomy has been supposed to increase the risk of surgical resection in CD^[24], while some authors failed to find an association with an increased disease severity^[25]. In UC, appendectomy not only decreases the risk of developing disease, but it also seems a protective factor against developing severe disease and reduces the need for colectomy^[22,26].

The tolerability and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in an IBD setting have been reviewed recently. Conventional NSAIDs may cause clinical relapse in about 20% of patients with quiescent disease^[27]. Some studies suggest that cyclooxygenase-2-selective NSAIDs, in particular celecoxib and etoricoxib, do not lead to exacerbations

of disease, but these data need to be validated with further randomized controlled trials^[28]. Generally, guidelines suggest a prudent use of NSAIDs in IBD patients.

As regards estrogens, a quite old prospective investigation showed that the current or former use of oral contraceptive (OC) pills leads to an increase risk for CD relapse (HR = 3.0, 95%CI: 1.5-5.9, $P < 0.001$)^[20]. In contrast, no evidence of a connection between prior or current usage of OC was found for UC patients in the only literature-reported study that has assessed this association^[15]. For hormone replacement therapy, an inverse association with IBD activity as a whole has been reported (HR = 0.18, 95%CI: 0.04-0.72, $P = 0.001$)^[29]. However, these results have not been validated by other studies and could suffer from bias due to patients’ age, different dosages and estrogen formulations.

Antibiotics could rationally play a role in defining the risk of relapse according to the way they influence the composition of intestinal microbiota. General antibiotic use has been documented to prevent CD relapse when compared with placebo (RR of relapse = 0.62, 95%CI: 0.46-0.84); all antibiotic combinations studied had some antimycobacterial properties. On the contrary, antibiotic administration in order to prevent UC relapse did not influence long-term relapse rates^[30].

In both UC and CD, patients under conditions of low stress and with good coping strategies (the capacity to modulate the effects of life stressors on illness experience) were least likely to suffer relapse^[31,32]. Particularly, relapse was positively associated with both stress (HR = 4.5, 95%CI: 1.9-10.7, $P < 0.001$) and coping strategies (HR = 1.9, 95%CI: 1.2-2.8, $P = 0.004$)^[32]. On the contrary, no association was found between disease relapse and depression in UC patients^[31].

MICROBIOTA

Intestinal microbiota seems to play a role in the pathogenesis of IBD. The currently accepted hypothesis is that a disruption of tolerance towards the commensal microbiota is produced in an individual with genetic vulnerability^[33]. Dysbiosis, defined as a reduction in bacterial biodiversity resulting in fewer bacteria with anti-inflammatory properties compared with healthy controls, has been observed in IBD^[34]. Potentially, gut microbiota can drive pathogenicity throughout an expansion of “pro-inflammatory” species or a reduction in the protective compounds of the microbiota^[35]. Several studies have reported that members of the Bacteroidetes and Firmicutes phyla were reduced in IBD^[36]; in contrast, a greater relative abundance in Enterobacteria, mostly *Escherichia coli* was observed^[37]. Among Firmicutes, *Faecalibacterium prausnitzii*, a butyrate-producing bacteria, seems to have anti-inflammatory properties and several reports have demonstrated a decrease in population of this

bacteria in patients with CD^[36,38].

Only a small number of studies have evaluated the role of gut microbiota in predicting clinical relapse in IBD. It has been demonstrated that a low proportion of *F. prausnitzii* in resected ileal mucosa from CD patients was associated with higher risk of post-operative recurrence^[38]. Furthermore, Rajca *et al.*^[39] have recently analysed fecal microbiota of 33 CD patients and found that a decrease in Firmicutes (in particular in *F. prausnitzii*) correlated with the time to relapse after infliximab withdrawal, so a deficit in some bacterial group, such as *F. prausnitzii*, may represent a predictive factor for relapse. Also, in UC patients, quantitative variations in different species of Lactobacillus have been identified between patients with relapse and patients in remission^[40]. In particular, Varela *et al.*^[41] analysed a wide cohort of UC patients in remission and demonstrated a consistent decrease of *F. prausnitzii*; a subsequent subanalysis of the cohort showed a more significant decrease in that bacterial species when patients had suffered a relapse in the previous 12 mo. The authors found that low levels of *F. prausnitzii* could be associated with a four-fold increase in the risk of relapse.

These findings underscore the interest of testing whether increasing the *F. prausnitzii* population in the gut microbiota would be a useful strategy for maintaining remission in IBD patients. In that case, restoring normobiosis in IBD patients could be a new goal for optimal management.

GENETIC PREDICTORS

No differences in disease behaviour have been observed when comparing familial IBD (that is, having a first-degree relative with the disease) and sporadic IBD. As such, disease severity is unaffected by family history^[42]. Despite this, familial cases are usually diagnosed at younger age and have an increased risk of extraintestinal manifestations and proving refractory to medical therapy^[43,44]. A family history of CD increases the risk of subsequent CD after ileo-pouch anal anastomosis (IPAA)^[45].

With the arrival of the genome-wide association study era, the ambition of identifying genetic prognostic factors in IBD has become somewhat attractive. The main quality of these markers is their long-term stability and the fact that they are already present not only at disease onset, but even earlier. The presence of the NOD-2/CARD15 polymorphism has been linked to more aggressive clinical course of CD; *i.e.*, higher risk of intestinal strictures, earlier need for surgery, reduced postoperative disease-free interval^[46]. Individuals carrying an increasing number of risk alleles in NOD2, IBD5 locus, DLG5, ATG16L1 and IL23R genes are more likely to experience a severe disease course. In particular, mutations in the ATG16L1 (autophagy-related 16-like 1) gene, encoding for a protein that

participates in autophagy, have been associated both with stricturing disease and perianal involvement in CD^[47]. Polymorphisms in multidrug resistance 1 gene (MDR1) were supposed to determine a more severe IBD and influence refractoriness/sensitiveness to medical therapy^[48].

LABORATORY MARKERS

Serological antibody markers

Several immune-mediated antibodies have been described in IBD. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) can help to differentiate CD from UC, particularly when used in combination, as ASCA are mainly associated to CD, while pANCA are linked to UC^[49,50]. Reactivity to ASCA was predictive of an aggressive disease phenotype; in particular it has been associated with early CD onset, fibrostenosing/penetrating CD behaviour and a need for CD-related surgery^[51,52]. In CD patients, pANCA has been linked to less severe disease, UC-like disease and minor risk of small bowel complications^[53]. In UC, pANCA are associated with a more severe disease course and need for surgery. In patients who undergo total proctocolectomy, higher levels of p-ANCA in the pre-surgical situation predict an increased risk of chronic pouchitis after IPAA^[54]. Bitton *et al.*^[15] reported that higher pANCA titres ($P = 0.02$) and total ANCA titers ($P = 0.03$) were significantly predictive of relapse only in univariate time-dependent analysis; no significance was observed in multivariate analysis. However, reliability of these antibodies in assessment of disease activity has not been found, and the entity of immune response to ASCA or pANCA has an inconsistent role in predicting disease relapse^[50]. In last years, the role of serum granulocyte macrophage colony-stimulating factor auto-antibody (GM-CSF Ab) in identifying IBD patients at risk of disease relapse at an early stage has been investigated, showing promising results both in UC and in CD^[55].

More recently, in addition to ANCA and ASCA, antibodies against specific bacterial wall products have gained increasing interest for their ability to help gastroenterologists in diagnosis, disease stratification and behaviour in IBD (antibodies to the *Escherichia coli* outer-membrane porin C - OmpC, anti-*Pseudomonas* associated sequence I2 and anti-bacterial Cbir1 flagellin). In particular, reactivity to ASCA, OmpC, anti-I2 and Cbir1 has been associated with with early CD onset, fibrostenosing and penetrating CD and need for early small bowel surgery^[52].

New anti-glycan antibodies, including anti-chitobioside IgA, anti-mannobioside IgG, anti-laminaribioside IgG, anti laminarin (anti-L) and anti-chitine (anti-C) have been recently added to the armamentarium of serologic markers in IBD. Anti-glycan antibodies are associated with a progression

Table 2 C-reactive protein as predictor of relapse in inflammatory bowel diseases patients

	No. Pt	No. R	Relapse rate	Mean CRP values R	Mean CRP values NR	P value
Brignola <i>et al</i> ^[5] , 1986						
CD	41	17	41%	2.2 mg/dL	0.7 mg/dL	0.010
Tibble <i>et al</i> ^[66] , 2000						
CD	43	25	58%	13.1 mg/L	9.1 mg/L	0.100
UC	37	19	51%	3 mg/L	9.7 mg/L	0.400
Bitton <i>et al</i> ^[15] , 2001						
UC	74	27	36.5%	0.08 mg/dL	0.25 mg/dL	NS
Costa <i>et al</i> ^[67] , 2005						
CD	38	15	39%	8 mg/L	6 mg/L	0.373
UC	41	19	46%	5 mg/L	4.5 mg/L	0.450
D'Inca <i>et al</i> ^[65] , 2008						
CD	65	20	31%	5.49 mg/L	3.13 mg/L	0.050
UC	97	37	38%	3.15 mg/L	3.08 mg/L	0.690
García-Sánchez <i>et al</i> ^[69] , 2010						
CD	66	18	27%	4.6 mg/L	5.6 mg/L	0.790
UC	69	21	31%	3.8 mg/L	1.7 mg/L	0.060
Kallel <i>et al</i> ^[62] , 2010						
CD ¹	53	10	18.9%	34 mg/L	4 mg/L	< 0.001
Naismith <i>et al</i> ^[70] , 2014						
CD	45	5	11%	2	2.1	0.539

¹Small bowel CD patients excluded. R: Relapsers; NR: Non relapsers; CRP: C reactive protein; CD: Crohn's disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases.

Table 3 Erythrocyte sedimentation rate as predictors of relapse in inflammatory bowel diseases patients

	No. Pt	No. R	Relapse rate	Mean ESR values R (mm/h)	Mean ESR values NR (mm/h)	P value
Brignola <i>et al</i> ^[5] , 1986						
CD	41	17	41%	24	9	0.0006
Tibble <i>et al</i> ^[66] , 2000						
CD	43	25	58%	21	13	0.200
UC	37	19	51%	13	20	0.200
Bitton <i>et al</i> ^[15] , 2001						
UC	74	27	36.5%	13.8	11	NS
Costa <i>et al</i> ^[67] , 2005						
CD	38	15	39%	20	15	0.077
UC	41	19	46%	15	11	0.056
D'Inca <i>et al</i> ^[65] , 2008						
CD	65	20	31%	25	15	0.005
UC	97	37	38%	14	11	0.690
García-Sánchez <i>et al</i> ^[69] , 2010						
CD	66	18	27%	17.5	16.2	0.230
UC	69	21	31%	14.1	7.6	0.180

R: Relapsers; NR: Non relapsers; ESR: Erythrocyte sedimentation rate; CD: Crohn's disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases.

to a more aggressive disease course and a higher risk for IBD-related surgery^[56,57]. Similarly to ANCA and ASCA, these promising biomarkers may help clinicians to identify certain IBD patient subgroups according to disease phenotype and risk of complications, but so far they are not suitable for prediction of relapse in the routine clinical practice.

Serological inflammatory markers

The potential role of inflammatory markers in predicting IBD relapse has been widely investigated, with special reference to C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Tables 2 and 3). Other laboratory markers, including leucocyte and platelet count, haemoglobin, albumin, α_1 -acid

glycoprotein, fibrinogen, lactoferrin, β_2 -microglobulin, α_2 -globulin, α_1 -antitrypsin have been studied less extensively, showing less consistent results as a whole.

Brignola *et al*^[58] observed that acid α_1 -glycoprotein, CRP, ESR, α_1 -antitrypsin and white blood cell count, as well as being altered during clinically active phases, may also be abnormal in about 50% of CD patients in remission. On the basis of these findings, they assumed that altered laboratory parameters in patients in apparent clinical remission - in particular, higher levels of α_1 -glycoprotein, α_2 -globulin, ESR, CRP and α_1 -antitrypsin - may reflect the early stage of subclinical inflammation of disease. Thus, these patients in remission phase might run a greater risk of clinical relapse within one-/two-year period than those

in clinical remission with normal laboratory findings^[5]. A simplified prognostic index ("New Index") was developed with the aim of predicting CD relapse within 18 mo, finding a relapse rate of 75% in those patients with at least one of the laboratory tests deranged (*i.e.*, α_1 -glycoprotein > 130 mg/dL, α_2 -globulins > 9.0 gm/L or ESR > 40 mm/h) vs 13% in those with normal test results^[59]. Another study^[60] confirmed that serum CRP is a valid marker in aiding prediction of CD course and in contributing to risk stratification among subgroups of patients. The likelihood of relapse after 2 years of participation was higher in the subgroup of patients who presented increased CRP levels compared with those with normal CRP at baseline. Many years later, the GETAID group^[61] proposed a simple binary biological score for predicting short-term relapse in CD patients. They selected only two predictive inflammatory markers of relapse: CRP > 20 mg/L and ESR > 15 mm/h. A positive score (at least one of the two markers raised) was associated with 8-fold increase risk in relapse compared with patients negative for both markers (95%CI: 2.8-22.9; score sensitivity and specificity: 89% and 43% respectively). Assuming a 10% relapse rate every 6 wk, they observed negative and positive predictive values of 97% and 15%, respectively, suggesting that normal CRP and ESR could almost certainly rule out relapse in the next six weeks.

Kallel *et al.*^[62] reported that CRP at baseline is a predictive factor for CD relapse (cut off levels 34 mg/L, risk of relapse 7.6). High-sensitivity (hs)-CRP was able to predict short- and medium-term relapse during the follow up, in patients hs-CRP positive at diagnosis. The predictive potential of hs-CRP was limited to those patients hs-CRP-positive at diagnosis^[63].

CRP levels were also found to be an independent risk factor both for colectomy in extensive UC at diagnosis (when above 23 mg/L) and for intestinal resection in CD involving the terminal ileum (when above 53 mg/L); however, in the same study, no association was found between the risk of relapse and CRP levels at diagnosis in patients with UC or CD as a whole, or in any subgroup according to disease localization^[64]. Another negative study comes from the results by D'Incà *et al.*^[65], where the predictive role of CRP seemed inconsistent for both UC and for CD patients. These authors postulated that ESR (and not CRP) could have a significant role in predicting clinical relapse in CD patients only, with a 72% sensitivity and an 85% specificity (cut-off 25 mm/h).

Nevertheless, neither ESR nor CRP values were found to be useful in predicting relapse in IBD as a whole in several studies primarily focusing on the prognostic value of fecal markers^[66-70]. In the prospective, single-centre study by García-Sánchez *et al.*^[69], median ESR (17.5 mm/h) and CRP (4.6 mg/L) in the CD relapsed group did not differ significantly ($P = 0.23$ for ESR, $P = 0.79$ for CRP) from that in the non-relapsed group (ESR 16.2 mm/h, CRP 5.6 mg/L), nor

there was a significant difference in the median ESR or CRP values ($P = 0.18$ for ESR; $P = 0.06$ for CRP) in the relapsed and non-relapsed UC patients (ESR 14.1 mm/h vs 7.6 mm/h; CRP 3.8 mg/L vs 1.7 mg/L). In agreement with these results, Gisbert *et al.*^[68] found that mean ESR and CRP in the IBD relapse group did not differ significantly from that in the non-relapse group.

The explanations for this conflicting data regarding the role of CRP in predicting IBD relapse may be its short "half life" and a known genetic CRP polymorphism in the general population that can reach a 20% rate^[71].

Other laboratory indices, including plasma cytokines - interleukin (IL)-1 β , IL-2, IL-6, IL-8, IL-10, IL-16, IL-2 soluble receptor, tumor necrosis factor- α (TNF- α), TNF- α soluble receptor, INF- γ - have been analysed, examining their potential predictive role. High soluble IL-2 receptor serum level was found to be strongly predictive of CD relapse^[72]. The same group showed that IL-6 serum level had great potential to predict the time-to-relapse in quiescent CD patients, alone or in association with other biological parameters such as α_1 -glycoprotein or soluble IL-2 receptor serum level. In particular, patient with an IL-6 serum level above 20 pg/mL had a 17-fold chance of relapse within 1-year period ($P < 0.001$)^[73].

In UC patients, higher IL-8 levels in the rectal mucosa were significantly associated with relapse, while no correlation was found for IL-1 β , IL-6 and TNF- α levels in rectal mucosa, conventional blood markers or for plasma cytokines (IL-1 β , IL-6, IL-8 and TNF- α). Thus, local IL-8 has been proposed as an additional objective tool for assessment of relapse^[74].

In contrast with the previous works, other authors failed to demonstrate a connection between detection/concentration levels of cytokines and the risk of IBD relapse, concluding that these systemic cytokines have little predictive value both in UC and CD patients^[15,75]. Bitton *et al.*^[15] found no evidence that serum IL-1 β , IL-6 and IL-15 predict relapse in UC ($P = NS$). The detection and baseline concentrations of the various cytokines tested (TNF- α , TNF- α -R1 and R2, IL-16, IL-1 β , IL 2, IL-R2, IL-6, IL-10, and IFN- γ) in a prospective study including 135 patients in clinical remission (66 CD and 69 UC patients; relapse rate: 30%) were not shown to be associated with the risk of relapse^[75]. Since the results are conflicting, no valid reasons exist to refer to these plasma cytokines, instead of cheaper serum markers such as CRP and ESR.

INTESTINAL PERMEABILITY

Increased intestinal permeability (IP) has been documented in IBD patients. It remains unclear whether barrier dysfunction precedes disease or results from active inflammation, however it is assumed that the intestinal tight-junction barrier is dynamically regulated by cytokines and pathogens.

The lactulose/mannitol test is frequently used

for investigating small intestinal permeability. The permeability index is calculated as the ratio of relative lactulose/relative mannitol urinary excretion. $^{51}\text{Cr-EDTA}$ is another common compound used to test small bowel permeability.

Elevated IP has also been found in clinically inactive CD patients. Consequently, permeability testing has been proposed as a non-invasive indicator of subclinical disease, preceding overt clinical relapse. Permeability testing with lactulose/mannitol has been demonstrated to be reliable in predicting relapses of CD within 1 year, with a PPV > 60%^[76]. In particular, the vast majority of studies that focused on IP as a predictor of disease relapse showed an increase in relative risk (RR) of relapse within 1 year for patients with increased sugar permeability ($3.1 < \text{RR} < 18$)^[66,77-80]. Only the study with $^{51}\text{Cr-EDTA}$ failed in revealing IP to be a useful predictor of relapse in patients with small intestinal CD^[81].

Permeability testing is not recommended in patients with isolated colonic involvement, consequently its application as a predictor tool is not feasible in the UC setting. It should be considered that permeability test is rather unspecific, as several non-IBD related conditions could increase IP (infection, NSAIDs or alcohol), resulting in a decrease of the positive predictive value.

ENDOSCOPY

In a retrospective study, during a median follow-up period of 52 mo, the rate of colonic resection among the 102 patients included with active colonic or ileo-colonic CD was significantly higher in patients who exhibited deep and extensive ulcerations at colonoscopy than in those without such severe endoscopic lesions (RR = 5.43, 95%CI: 2.64-11.18)^[82,83]. In UC patients affected with severe acute attacks, the presence of deep ulcerations and extensive disease seems to be predictive of more aggressive disease, failure of medical treatment and a higher rate of colectomy^[84].

The achievement of mucosal healing (MH) after induction therapy has been supposed to have a good prognostic value both in UC and CD. MH is thought to be associated with a generally favourable outcome of disease, including sustained clinical remission, treatment efficacy, reduced rate of surgery and hospitalizations^[85]. Documented MH obtained with immunosuppressant or anti-TNF α agents is predictive of sustained clinical remission in patients with early stage CD and it is linked to a decreased risk of surgery in the long term^[86].

Also, for UC, MH is associated with a better outcome, with a decreased rate of relapse and a reduced risk of major surgery^[85,87].

Although suggestive for remission, normal mucosal appearance at routine colonoscopy might not reveal persistence of microscopic mucosal abnormalities, smouldering histopathological inflammation responsible for later relapse^[1].

Magnifying colonoscopy (MCS) examinations seems superior to conventional endoscopy in evaluating the inflammatory activity of UC, because it better correlates with histopathological grade^[88,89]. Moreover, altered mucosal pattern as defined by high-resolution video-magnifying examination may predict exacerbations in UC patients in clinical remission^[89]. Fujiya *et al.*^[89] reported that UC patients showing minute defects of epithelium during clinical remission frequently had a relapse within a short period (6 mo), compared with those without these findings ($P = 0.02$). Data published by Watanabe *et al.*^[90] confirmed these findings. In another study by Ando *et al.*^[91], 112 UC patients in remission were followed up until relapse, or a maximum of 12 mo. MCS was shown to be a significant predictor of future flares and the rate of relapse within 12 mo was found to increase with increasing MCS grade (0% for grade 1, 19% for grade 2, 43% for grade 3). They suggested a greater accuracy of MCS grading in predicting disease relapse compared to histological grade. Indeed, while biopsy specimens refer to a specific and limited mucosal portion, magnifying colonoscopy allows the observation of a more extended and representative area. In contrast with these findings, other authors reject the role of advanced endoscopy in predicting relapse over a 1-year period in patients with quiescent UC. Seventeen (27%) out of 64 UC patients with sustained clinical remission experienced a flare during the follow up period. Neither the mucosal pit pattern nor vascular pattern assessed through chromoendoscopy (CE) and narrow band imaging (NBI) was significantly different between relapsers and non-relapsers ($P = 0.69$ for CE pit pattern; $P = 0.57$ for NBI pit pattern; $P = 0.72$ for NBI vascular intensity)^[92].

Confocal laser endomicroscopy (CLE) with intravenous fluorescein has been proven to accurately detect and quantify *in vivo* intramucosal changes during the clinical and endoscopic remission phase. These changes are potentially predictive of disease relapse, making CLE an attractive tool in IBD management^[93-95]. Kiesslich *et al.*^[93] devised a simple endomicroscopic grading system for *in vivo* localization of local barrier dysfunction, defined as a discontinuity in the epithelium due to epithelial cell shedding (Watson grade). They prospectively followed up 58 IBD patients in clinical remission (47 UC, 11 CD; CAI ≤ 1 , CDAI ≤ 150) within a 12-mo period. Local barrier dysfunction in the small intestine of IBD patients, that is fluorescein leakage and microerosions (functional or structural defects identified as Watson grade II or III), was significantly associated with a higher rate of relapse ($P < 0.001$) compared with Watson grade I (normal, physiological cell shedding into the lumen). The sensitivity, specificity and accuracy of this grading system to predict relapse were 62.5%, 91.2% and 79%, respectively. Similarly, other researchers found that UC patients in clinical remission with active inflammation at CLE (grade C or D) were more likely

to suffer a flare than those with a lower grade (normal or chronic inflammation; grade A or B respectively). Grade C and D (*i.e.*, acute inflammation) have a sensitivity of 64%, specificity of 88.9% and accuracy 74.4%, in predicting relapse^[95].

HISTOLOGY

In CD, studies investigating the association between histological features and the risk of relapse are limited to the post-operative setting^[96,97]. Literature is focused mainly on UC. Riley *et al.*^[11] showed that acute inflammatory indicators are associated with a two- to three-fold increased risk of UC relapse during a 12 mo follow up. Specifically, six histological features were assessed in this study: acute inflammatory cell infiltrate (polymorphonuclear cells in the lamina propria), crypt abscesses, mucin depletion, surface epithelial integrity, chronic inflammatory cell infiltrate (round cells in the lamina propria), and crypt architectural irregularities. They reported a relapse rate of 52% among patients showing an acute inflammatory cell infiltrate on rectal biopsy specimens, while in the absence of such an infiltrate only 25% of the patients experienced a flare ($P = 0.02$). Similarly, relapse rates were considerably higher in the presence than in the absence of crypt abscesses (78% vs 27%, $P < 0.005$), mucin depletion (56% vs 26%, $P < 0.02$), and breaches in the surface epithelium (75% vs 31%, $P = 0.01$). On the other hand, neither a chronic inflammatory cell infiltrate nor crypt architectural abnormalities were of prognostic importance on subsequent relapse rate. Bitton *et al.*^[15], reported data taking into account basal plasmacytosis, that is a dense infiltration of plasma cells extending into the lower one third of the lamina propria, an area where these cells are usually absent or barely present. The evidence of basal plasmacytosis on rectal biopsy specimens lead to a greater short-term relapse risk in UC patients ($P = 0.003$, HR = 4.5) even if patients receiving rectal enemas or suppositories were allowed to participate in this study.

The presence of basal plasmacytosis ($P = 0.0007$, OR = 5.13) and Geboes Index (GI)^[98] ≥ 3.1 ($P = 0.007$) predicted relapse in UC patients with endoscopically inactive disease^[99]. Data recently published by Popp *et al.*^[100] confirmed these findings.

In contrast, baseline histology features evaluated with Riley classification^[11] were not statistically different between relapsing and non-relapsing UC patients in a recent study by Jauregui-Amezaga *et al.*^[92] and basal plasmacytosis did not appear as a predictor of relapse ($P = 0.07$). It was found in 38 (59%) patients but only 7 of these relapsed (18%), while 10 of the 24 (38%) patients without basal plasmacytosis relapsed.

FECAL MARKERS

In recent decades, a number of stool biomarkers

have been evaluated for their potential in the IBD scenario (fecal calprotectin, lactoferrin, S100A12, Indium 111-labeled leukocytes, α 1-antitrypsin, α 2-macroglobulin, myeloperoxidase, PMN-elastase). Their utility has been studied in relation to diagnosing, establishing the activity of the disease, monitoring treatment response and predicting clinical relapse^[101,102]. Fecal tests have further advantages of being cheap, easy to perform, safe, simple for the patient and therefore very useful in clinical practice. Moreover, they have excellent stability in feces being resistant to bacterial degradation and stable in stool at room temperature for up to 7 d^[103]. Most of them have only a low diagnostic performance, so their clinical role is doubtful. As regards the utility in prediction of clinical relapse, the accuracy of fecal calprotectin (FC), lactoferrin and S100A12 has been evaluated.

Fecal calprotectin

FC is a calcium-binding protein derived from neutrophils, monocytes and reactive macrophages^[104]. The FC test has been shown to correlate with both endoscopic and microscopic evidence of gastrointestinal inflammation in IBD^[102], reflecting the migration of neutrophils through the inflamed bowel wall to the colonic/rectal mucosa.

In several clinical studies with both adults and children, elevated FC concentrations were found despite clinical remission^[66,105-107]. It appears that FC can detect subclinical mucosal inflammation and thus may identify patients at risk of relapse (Table 4).

As shown in the STORI study, elevated FC seemed to predict relapse after stopping infliximab therapy in patients with CD. A FC concentration of over 300 μ g/g was an independent risk factor associated with disease relapse^[108]. A recently published meta-analysis of six prospective studies showed a pooled sensitivity of 78% and a specificity of 73% for FC in predicting IBD relapse^[109]. The test results were comparable between UC and CD^[110].

Previously, Costa *et al.*^[67] reported a twofold and 14-fold increased risk of relapse in CD and UC patients respectively, who had a baseline level of FC higher than 150 μ g/g at inclusion. Sensitivity was high for both CD (87%) and UC (89%), but specificity was much lower in the case of CD (43%) compared with UC (82%).

FC appears to be less useful in predicting relapse in patients with ileal CD compared with colonic/ileocolonic CD or UC^[65,68,69]. For this reason, some authors stress the need of stratification of CD patients according to phenotypical pattern to improve the predictive capacity of FC in CD^[68,69]. The good predictive value of FC was confirmed when CD patients with only small bowel involvement were excluded, with the aim to obtain a more homogeneous group. Patients with colonic or ileo-colonic CD in remission and FC levels above 340 μ g/g presented an almost 19-fold greater risk of

Table 4 Fecal calprotectin as a predictor of relapse in inflammatory bowel disease patients

IBD type	Criteria for defining relapse	No. Pt	No. R	Relapse rate	Mean FC values R	Mean FC values NR	P value	FC cut off	Se	Spe	PPV	NPV	HR7
Tibble <i>et al</i> ^[66] , 2000													
CD	CDAI > 150	43	25	58%	122 mg/L	41.5 mg/L	< 0.0001						
	ΔCDAI > 100				(610 μg/g)	(220 μg/g)							
UC	HBI > 4 ΔHBI > 2	37	19	51%	123 mg/L	29 mg/L	< 0.0001						
IBD		80	44	55%	123 mg/L	32 mg/L	< 0.0001	50 mg/L (250 μg/g)	90	83			
Costa <i>et al</i> ^[67] , 2005													
CD	CDAI > 150	38	15	39.5%	220.1 μg/g	220.5 μg/g	0.395	150 μg/g	87	43	50	83	2.20
UC	UCAI > 4	41	19	46.3%	220.6 μg/g	67 μg/g	< 0.0001	150 μg/g	89	82	81	90	14.40
IBD		79	34	43%									
D'Inca <i>et al</i> ^[65] , 2008													
CD	CDA ≥ 150 ΔCDAI > 50	65	20	31%	207 mg/kg	88 mg/kg	0.055	130 mg/kg	65	62	44	80	1.70
Colonic CD					176.7 mg/kg	75.1 mg/kg	0.041						
UC	ET > 4	97	37	38%	190 mg/kg	49 mg/kg	0.001	130 mg/kg	70	70	60	79	2.40
IBD		162	57	35.2%				130 mg/kg	68	67	52	79	
Gisbert <i>et al</i> ^[68] , 2009													
CD	CDAI > 150	89	13	14.6%	266 μg/g	145 μg/g	0.002	169 μg/g	69	76			
UC	TW > 11	74	13		213 μg/g	126 μg/g	0.030	164 μg/g	69	74			
IBD		163	26	16%	239 μg/g	136 μg/g	< 0.001	167 μg/g	69	75	35	93	2.80
García-Sánchez <i>et al</i> ^[69] , 2010													
CD	CDAI ≥ 150	66	18	27%	524 μg/g	123 μg/g	< 0.010	200 μg/g	80	65	46	88	4.35
UC	TW ≥ 11	69	21	31%	298 μg/g	105 μg/g	< 0.010	120 μg/g	81	63	49	88	6.48
IBD		135	39	30%	444 μg/g	112 μg/g	< 0.010	150 μg/g	75	68	49	68	
Kallel <i>et al</i> ^[62] , 2010													
CD ¹	CDAI > 150 ΔCDAI > 100	53	10	18.9%	380.5 μg/g	155 μg/g	< 0.001	340 μg/g	80	90.7			18.80
Naismith <i>et al</i> ^[70] , 2014													
CD	Treatment	92	10	11%	414 μg/g	96 μg/g	0.005	240 μg/g	80	74.4	27.6	96.8	12.18
Colonic CD	modification,	35	4		424 μg/g	187	0.160						
Ileal CD	progression, disease phenotype, hospitalization, surgery	16	3		371 μg/g	57	0.057						
Yamamoto <i>et al</i> ^[74] , 2014													
UC		80	21	26%	173.7 μg/g	135.5 μg/g	0.020	170 μg/g	76	76			7.23
Scaioli <i>et al</i> ^[111]													
UC	SCCAI > 3 Mayo > 1	74	20	27%	218 μg/g	48 μg/g	< 0.010	193 μg/g	65	98	92	88	

¹Small bowel CD patients excluded. 12-mo follow-up period in all the studies cited; FC assay was Calprest for all the studies cited, except in the study by Tibble *et al*^[66] (Roseth). R: Relapsers; NR: Non relapsers; FC: Fecal calprotectin; Se: Sensibility; Spe: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; HR: Hazard ratio; CD: Crohn's disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases; HBI: Harvey Bradshaw Index; CDAI: Crohn's disease activity index; CAI: Colitis activity index; TW: Modified Truelove-Witt; SCCAI: Simple Clinical Colitis Activity.

relapse than those with lower concentrations^[62].

A large prospective study of 92 CD patients provides evidence that adults with quiescent CD with an FC level below 240 μg/g were unlikely to relapse within 12 mo (NPV 96.8%), while those with a FC level of 240 μg/g or above were associated with greater likelihood of relapse within 12 mo, 12.28 times higher than lower values ($P = 0.002$)^[70].

As regards the performance of FC in UC populations, several authors identified cut off values ranging from 120 μg/g to 250 μg/g as being able to predict clinical relapse with good accuracy^[65-69,110].

In parallel with this data, we have recently reported that an FC cut off value of 193 μg/g is able to predict clinical relapse in 74 UC patients in clinical remission with a Mayo endoscopic sub-score ≤ 1 followed up

for one year (89% accuracy, 65% sensitivity, 98% specificity)^[111].

Tibble *et al*^[66] found that FC levels in patients with an early relapse (< 1 mo) were somewhat higher than those in patients who relapsed later, but no statistically significant difference was noticed. No differences were found in the predictive capacity of this marker according to disease extent (distal or extensive colitis)^[69].

FC has been evaluated also as a predictor of relapse in IBD patients under maintenance Infliximab therapy^[112] finding a cut off of 160 μg/g able to predict clinical relapse with a sensitivity of 91.7% and a specificity of 82.9%. Previously Molander *et al*^[113] reported that a normal FC after induction therapy with Infliximab or Adalimumab is a good predictor of

clinical response to the scheduled therapy. Recently, in a prospective multicenter study, De Vos *et al.*^[114] found in eighty-seven UC patients in clinical remission after Infliximab maintenance therapy, that patients who flared had FC median > 300 mg/kg already three months before the flare. Two consecutive FC measurements of > 300 mg/kg with 1-mo interval were identified as the best predictor of a flare, increasing the specificity greater than that of a single measurement (specificity of 100% vs 93%).

Due to the FC variability in a day to day^[115,116] and also during the same day^[117,118] two measurements are suggested; the variation seems to be higher in patients with elevated concentration of FC^[119].

Lactoferrin

Lactoferrin is an iron-binding glycoprotein and a major component of the secondary granules of polymorphonuclear neutrophils. The excretion of lactoferrin in stool increases during intestinal inflammation, as leucocytes invade the mucosa^[119,120]. Similarly to FC, it is stable in stool for up to 4 d, thanks to its antibacterial activity and resistance to proteolysis^[121]. Results on the potential utility of fecal lactoferrin measurements at remission to predict clinical flares seem promising, both in CD and UC patients. It has been shown that fecal lactoferrin may rise significantly prior to a clinically evident relapse^[122].

A positive lactoferrin test was more frequent in relapsing than in non-relapsing IBD patients (62% vs 35%, $P < 0.05$). From another perspective, 10% of the patients with negative fecal lactoferrin test relapsed during follow-up, while this occurred in 25% of those having a positive test result ($P < 0.05$)^[68].

Limited to UC, assuming a cut-off value of 140 µg/g, lactoferrin showed lower sensitivity and specificity than FC in predicting UC relapse (67% and 68% vs 76% and 76%, respectively)^[110].

Patients with IBD experiencing clinical relapse within the next 2 mo showed significantly higher lactoferrin levels^[123]. In the study by Gisbert *et al.*^[68], lactoferrin had a 46% sensitivity and 61% specificity to predict relapses in UC and of 77% sensitivity and 68% specificity in CD.

S100A12

Neutrophil-derived S100A12, also known as calgranulin C, is a protein expressed by activated neutrophils. Several studies have demonstrated a correlation between mucosal inflammation and S100A12 levels in blood and feces^[124-126]. The role of S100A12 as a marker of future relapse in pediatric and adult IBD patients has been investigated in only one prospective study so far. A baseline fecal S100A12 level of > 0.5 mg/kg was significantly associated with clinical IBD relapse within 18 mo. Fecal S100A12 levels seemed to be already increased up to 6 mo before clinical relapse. In contrast, no differences were observed in

serum S100A12 levels between relapsers and non-relapsers^[127].

POST-OPERATIVE RECURRENCE IN CD

Surgical resection of the diseased bowel in CD is not curative, and approximately half of the patients require surgery within 10 years after diagnosis, despite the wide availability of immunosuppressive and anti-TNFα treatments^[128].

Active smoking status is a strong predictor of post-operative recurrence. In particular, patients who continue smoking after surgery have a 2-fold increased risk of clinical relapse, with a further increase in the risk according to the number of cigarettes smoked per day^[19,129]. History of repeated intestinal resection (more than twice) appears to be another undisputed predictor of postoperative recurrence^[130]. Penetrating disease behaviour, perianal disease, extensive bowel resection, short disease duration prior to surgery, non-colonic disease location and long duration are other established risk factors for postoperative recurrence, but their predictive value has been shown to be less consistent^[130]. The roles of young age at diagnosis and family history remain controversial^[2].

It has been demonstrated that low proportion of *F. prausnitzii* in resected ileal mucosa from CD patients was associated with higher risk of post-operative recurrence^[38].

Endoscopic findings with biopsy are unanimously considered a reliable predictor of subsequent clinical course and an ileocolonoscopy during the first post-operative year is highly recommended^[131].

As regards histological features, an "active disease" at the margin of resection, characterized by myenteric plexitis^[96], lymphatic vessel density in the proximal margin of resection and morphological analysis of Paneth cells, may predict post-operative recurrence^[98]. On the contrary, granulomas and chronic inflammation at the margin of resection seems to be less relevant as a predicting value^[97].

Since conventional endoscopy does not allow access to the small gut, wireless capsule enteroscopy is proposed but not widely used in this setting. Ionising radiation exposure limits the use of computed tomography enteroclysis, while magnetic resonance, perhaps the gold standard for imaging, remains of limited access^[132].

Fecal markers have been recently proposed, although "false positives" due to, for example, bile salt malabsorption may occur. Indeed, patients with low levels of FC and lactoferrin after resection are unlikely to have mucosal inflammation and cut-off values of > 50 µg/g and > 7.25 µg/g for FC and lactoferrin respectively have been considered to diagnose clinical post-operative CD recurrence^[133]. This evidence is supported by Orlando *et al.*^[134] who showed that FC at a concentration of > 200 mg/L at three months after

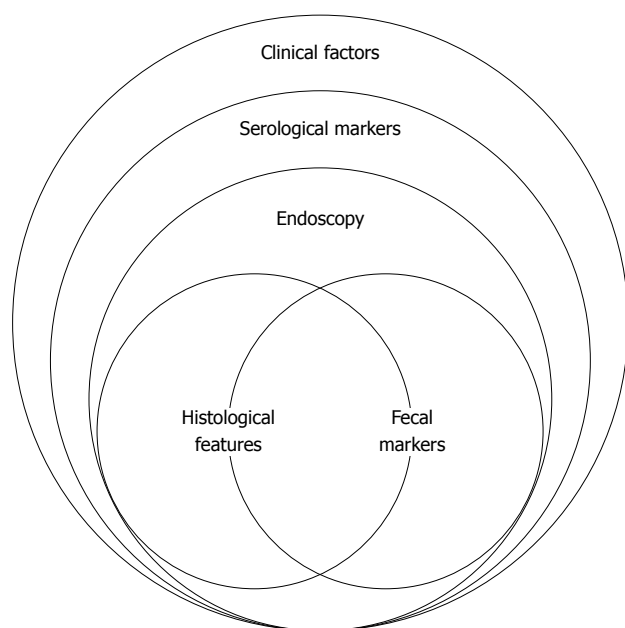


Figure 1 "Probing items" available for the clinicians to predict clinical relapse in inflammatory bowel diseases.

surgery can be an indication for colonoscopy in order to detect early endoscopic recurrence (sensitivity of 63% and specificity of 75%). A recent meta-analysis showed that FC is a useful marker in evaluating clinical and endoscopic recurrence in CD patients who had undergone previous surgical resection^[135]. The authors evaluated ten articles, finding a pooled sensitivity of 0.82 and specificity of 0.61 for assessing endoscopic recurrence and a pooled sensitivity of 0.59 and specificity of 0.88 for evaluating clinical relapse. Wright *et al.*^[136] in a large (135 patients), prospective, randomized, controlled trial evaluated the utility of serial measurements (month 6, 12 and 18 postoperatively) of FC, CRP and CDAI in predicting endoscopic recurrence after CD resection. Combined 6- and 18-mo FC levels correlated significantly with presence and severity of endoscopic recurrence, whereas CRP and the CDAI did not. A cut-off of FC > 100 $\mu\text{g/g}$ identified patients with endoscopic recurrence with 89% sensitivity and 58% specificity (NPV 91%).

Non-invasive biomarkers have substantial appeal in this setting because they can be repeated much more frequently than colonoscopy. Future studies should gather additional information to help to understand the optimal frequency to measure FC.

CONCLUSION

IBDs have a natural course characterized by relapsing and remitting phases. Disease flares occur in a random way and are mostly unpredictable. Prediction of relapse is a longstanding ambition of gastroenterologists, since it could have pivotal implications for future therapeutic strategies.

A "predictive" ideal marker should reveal inflam-

mation at a pre-symptomatic stage, and at the same time, it should be easy and rapid to perform, cheap, as minimally invasive as possible and reproducible between patients and laboratories.

Clinical variables, serological, fecal markers and genetic tests are available, but no single one of them is highly predictive when used alone. Of course, data obtained from endoscopy and histology are of great value, but their utilization as predictors of clinical relapse are strongly limited by their invasiveness. An overview of the "probing items" available for the clinicians is reported in Figure 1.

In the 80s, Brignola first understood the need of stratifying patients in remission on the basis of their risk of relapse, for improving the therapeutic management of patients, and a "New Index" containing a mixture of serological markers demonstrated its ability to predict clinical relapse in a reasonably long period of time. Also, he stressed the concept that inflammatory markers need to be coupled to clinical history as a complementary predictor of flare up risk.

The GETAID group embraced this idea and showed that clinical course of the disease can tell us a great deal of information, such as that a short interval since the previous relapse is associated with a poor prognosis and also that a biological predictive score can predict short-term maintenance of remission in patients with clinically inactive CD after recent weaning off steroids. The downside of this approach is that serological markers are not always displayed by patients, and also that they could be influenced by several extra-intestinal diseases; on the other hand, clinical manifestations suffer from subjectivity.

This tricky situation has been recently ameliorated by a new fecal marker, namely fecal calprotectin; an increasing body of evidence states its ability in mirroring mucosal inflammatory activity. A validated cut off value of FC for predicting IBD relapse is not yet well defined, however authors agree that different cut-offs should be considered according to the type of IBD and, among CD, subcategories of patients have to be distinguished according to disease location and extension. In general, higher cut off points have been noticed in CD than in UC.

Both in CD and in UC, we prefer to observe at least two measurements of FC above the cut-off point, as day-to-day variability in FC levels has been described.

In our opinion, in our daily clinical practice, validated prognostic scores should be elaborate, including a combination of the most promising markers, either clinical and biological. For that reason we propose an algorithm of current use in our daily practice, including both blood tests and faecal markers, enhanced by characteristics of the clinical history.

In CD setting, the presence of at least 2 among: young age at onset, extensive disease, perianal involvement, steroid requirement at the onset, short previous remission and history of previous more

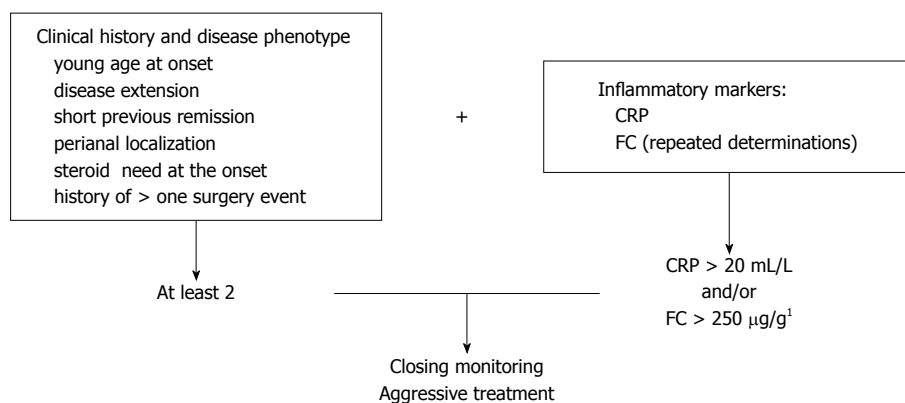


Figure 2 Algorithm to identify Crohn's disease patients with high risk of clinical relapse. ¹In at least 2 determinations. CRP: C reactive protein; FC: Fecal calprotectin.

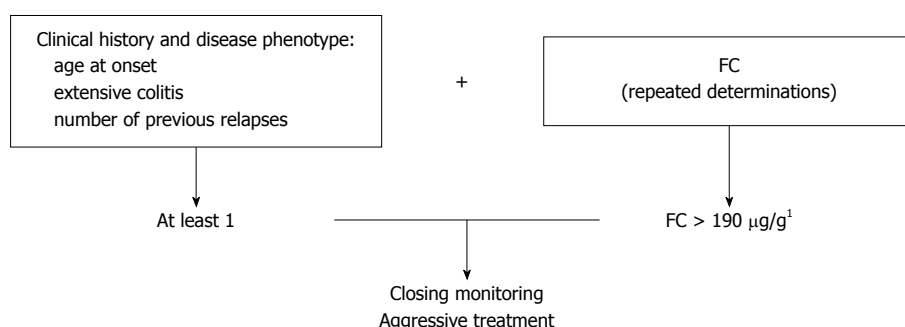


Figure 3 Algorithm to identify ulcerative colitis patients with high risk of clinical relapse. ¹In at least 2 determinations. FC: Fecal calprotectin.

than one surgery event, together with the presence of CRP > 20 mL/L and/or FC above 250 µg/g in at least two determinations, make a CD patients deserving aggressive treatment (Figure 2). Similarly, clinical history and disease extent have to be kept in mind when evaluating a patient affected by UC. We consider young age at onset, extensive colitis and the number of previous relapses as fundamental elements of clinical history that should be evaluated. The presence of at least one of the previous items and the measurement of an FC above 190 µg/g in at least two determinations, legitimize more aggressive therapy and close monitoring (Figure 3).

REFERENCES

- Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991; **32**: 174-178 [PMID: 1864537]
- Beaugerie L, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. *World J Gastroenterol* 2012; **18**: 3806-3813 [PMID: 22876031 DOI: 10.3748/wjg.v18.i29.3806]
- Yarur AJ, Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2011; **7**: 652-659 [PMID: 22298958]
- Louis E, Belaiche J, Reenaers C. Do clinical factors help to predict disease course in inflammatory bowel disease? *World J Gastroenterol* 2010; **16**: 2600-2603 [PMID: 20518080 DOI: 10.3748/wjg.v16.i21.2600]
- Brignola C, Campieri M, Bazzocchi G, Farruggia P, Tragnone A, Lanfranchi GA. A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease. *Gastroenterology* 1986; **91**: 1490-1494 [PMID: 3770373]
- Sahmoud T, Hochtin-Boes G, Modigliani R, Bitoun A, Colombel JF, Soule JC, Florent C, Gendre JP, Lerebours E, Sylvester R. Identifying patients with a high risk of relapse in quiescent Crohn's disease. The GETAID Group. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut* 1995; **37**: 811-818 [PMID: 8537053]
- Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006; **130**: 650-656 [PMID: 16530505]
- Solberg IC, Vatn MH, Høie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol* 2007; **5**: 1430-1438 [PMID: 18054751]
- Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. *Scand J Gastroenterol* 2008; **43**: 948-954 [PMID: 19086165]
- Wolters FL, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L, Langholz E, Politi P, Qasim A, Koutroubakis I, Tsianos E, Vermeire S, Freitas J, van Zeijl G, Hoie O, Bernklev T, Beltrami M, Rodriguez D, Stockbrügger RW, Moum B. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. *Gut* 2006; **55**: 1124-1130 [PMID: 16361306]
- Henriksen M, Jahnsen J, Lygren I, Aadland E, Schulz T, Vatn MH, Moum B. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol* 2007; **42**: 602-610 [PMID: 17454881]
- Farhi D, Cosnes J, Zizi N, Chosidow O, Seksik P, Beaugerie L, Aractingi S, Khosrotehrani K. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine (Baltimore)* 2008; **87**: 281-293 [PMID: 18794711 DOI: 10.1097/MD.0b013e318187cc9c]
- Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology

- and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- 14 **Hoie O**, Wolters FL, Riis L, Bernklev T, Aamodt G, Clofent J, Tsianos E, Beltrami M, Odes S, Munkholm P, Vatn M, Stockbrügger RW, Moum B. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007; **132**: 507-515 [PMID: 17258717]
 - 15 **Bitton A**, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MD, Stevens AC. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001; **120**: 13-20 [PMID: 11208709]
 - 16 **Langholz E**, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994; **107**: 3-11 [PMID: 8020674]
 - 17 **Solberg IC**, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, Bernklev T, Henriksen M, Sauar J, Vatn MH, Moum B. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009; **44**: 431-440 [PMID: 19101844 DOI: 10.1080/00365520802600961]
 - 18 **Martin TD**, Chan SS, Hart AR. Environmental factors in the relapse and recurrence of inflammatory bowel disease: a review of the literature. *Dig Dis Sci* 2015; **60**: 1396-1405 [PMID: 25407806 DOI: 10.1007/s10620-014-3437-3]
 - 19 **Reese GE**, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis* 2008; **23**: 1213-1221 [PMID: 18762954 DOI: 10.1007/s00384-008-0542-9]
 - 20 **Timmer A**, Sutherland LR, Martin F. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1998; **114**: 1143-1150 [PMID: 9618650]
 - 21 **Beaugerie L**, Massot N, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Impact of cessation of smoking on the course of ulcerative colitis. *Am J Gastroenterol* 2001; **96**: 2113-2116 [PMID: 11467641]
 - 22 **Radford-Smith GL**, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, Green A, Newman B, Florin TH. Protective role of appendectomy on onset and severity of ulcerative colitis and Crohn's disease. *Gut* 2002; **51**: 808-813 [PMID: 12427781]
 - 23 **Kaplan GG**, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. *Gut* 2007; **56**: 1387-1392 [PMID: 17494106]
 - 24 **Riegler G**, Caserta L, Esposito I, De Filippo FR, Bossa F, Esposito P, Russo MI, Carratù R. Worse clinical course of disease in Crohn's patients with previous appendectomy. *Eur J Gastroenterol Hepatol* 2005; **17**: 623-627 [PMID: 15879724]
 - 25 **Cosnes J**, Seksik P, Nion-Larmurier I, Beaugerie L, Gendre JP. Prior appendectomy and the phenotype and course of Crohn's disease. *World J Gastroenterol* 2006; **12**: 1235-1242 [PMID: 16534877 DOI: 10.3748/wjg.v12.i8.1235]
 - 26 **Cosnes J**, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. Effects of appendectomy on the course of ulcerative colitis. *Gut* 2002; **51**: 803-807 [PMID: 12427780]
 - 27 **Kvasnovsky CL**, Aujla U, Bjarnason I. Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease. *Scand J Gastroenterol* 2015; **50**: 255-263 [PMID: 25314574 DOI: 10.3109/00365521.2014.966753]
 - 28 **Miao XP**, Li JS, Ouyang Q, Hu RW, Zhang Y, Li HY. Tolerability of selective cyclooxygenase 2 inhibitors used for the treatment of rheumatological manifestations of inflammatory bowel disease. *Cochrane Database Syst Rev* 2014; **10**: CD007744 [PMID: 25340915 DOI: 10.1002/14651858.CD007744.pub2]
 - 29 **Kane SV**, Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 1193-1196 [PMID: 18177456 DOI: 10.1111/j.1572-0241.2007.01700.x]
 - 30 **Khan KJ**, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 661-673 [PMID: 21407187 DOI: 10.1038/ajg.2011.72]
 - 31 **Levenstein S**, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzzi C, Arcà M, Berto E, Milite G, Marcheggiano A. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000; **95**: 1213-1220 [PMID: 10811330]
 - 32 **Bitton A**, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, Cohen A, Vermeire S, Dufresne L, Franchimont D, Wild GE. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008; **57**: 1386-1392 [PMID: 18390994 DOI: 10.1136/gut.2007.134817]
 - 33 **Sartor RB**. Microbial influences in inflammatory bowel diseases. *Gastroenterology* 2008; **134**: 577-594 [PMID: 18242222 DOI: 10.1053/j.gastro.2007.11.059]
 - 34 **Frank DN**, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 2007; **104**: 13780-13785 [PMID: 17699621]
 - 35 **Seksik P**. [Gut microbiota and IBD]. *Gastroenterol Clin Biol* 2010; **34** Suppl 1: S44-S51 [PMID: 20889004 DOI: 10.1016/S0399-8320(10)70020-8]
 - 36 **Sokol H**, Seksik P, Furet JP, Firmesse O, Nion-Larmurier I, Beaugerie L, Cosnes J, Corthier G, Marteau P, Doré J. Low counts of *Faecalibacterium prausnitzii* in colitis microbiota. *Inflamm Bowel Dis* 2009; **15**: 1183-1189 [PMID: 19235886 DOI: 10.1002/ibd.20903]
 - 37 **Darfeuille-Michaud A**, Boudeau J, Bulois P, Neut C, Glasser AL, Barnich N, Bringer MA, Swidsinski A, Beaugerie L, Colombel JF. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. *Gastroenterology* 2004; **127**: 412-421 [PMID: 15300573]
 - 38 **Sokol H**, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangeat C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 2008; **105**: 16731-16736 [PMID: 18936492 DOI: 10.1073/pnas.0804812105]
 - 39 **Rajca S**, Grondin V, Louis E, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Paintaud G, Piver E, Allez M, Mary JY, Sokol H, Colombel JF, Seksik P. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 978-986 [PMID: 24788220 DOI: 10.1097/MIB0000000000000036]
 - 40 **Bullock NR**, Booth JC, Gibson GR. Comparative composition of bacteria in the human intestinal microflora during remission and active ulcerative colitis. *Curr Issues Intest Microbiol* 2004; **5**: 59-64 [PMID: 15460067]
 - 41 **Varela E**, Manichanh C, Gallart M, Torrejón A, Borrueal N, Casellas F, Guarner F, Antolin M. Colonisation by *Faecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2013; **38**: 151-161 [PMID: 23725320 DOI: 10.1111/apt.12365]
 - 42 **Henriksen M**, Jahnsen J, Lygren I, Vatn MH, Moum B. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. *Am J Gastroenterol* 2007; **102**: 1955-1963 [PMID: 17573793]
 - 43 **Halme L**, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 3668-3672 [PMID: 16773682 DOI: 10.3748/wjg.v12.i23.3668]
 - 44 **Haritunians T**, Taylor KD, Targan SR, Dubinsky M, Ippoliti A,

- Kwon S, Guo X, Melmed GY, Berel D, Mengesha E, Psaty BM, Glazer NL, Vasiliauskas EA, Rotter JI, Fleshner PR, McGovern DP. Genetic predictors of medically refractory ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 1830-1840 [PMID: 20848476 DOI: 10.1002/ibd.21293]
- 45 **Shen B**, Remzi FH, Hammel JP, Lashner BA, Bevins CL, Lavery IC, Wehkamp J, Fazio VW. Family history of Crohn's disease is associated with an increased risk for Crohn's disease of the pouch. *Inflamm Bowel Dis* 2009; **15**: 163-170 [PMID: 18798573 DOI: 10.1002/ibd.20646]
- 46 **Alvarez-Lobos M**, Arostegui JI, Sans M, Tassies D, Plaza S, Delgado S, Lacy AM, Pique JM, Yagüe J, Panés J. Crohn's disease patients carrying Nod2/CARD15 gene variants have an increased and early need for first surgery due to stricturing disease and higher rate of surgical recurrence. *Ann Surg* 2005; **242**: 693-700 [PMID: 16244543]
- 47 **Weersma RK**, Stokkers PC, van Bodegraven AA, van Hogezaand RA, Verspaget HW, de Jong DJ, van der Woude CJ, Oldenburg B, Linskens RK, Festen EA, van der Steege G, Hommes DW, Crusius JB, Wijmenga C, Nolte IM, Dijkstra G. Molecular prediction of disease risk and severity in a large Dutch Crohn's disease cohort. *Gut* 2009; **58**: 388-395 [PMID: 18824555 DOI: 10.1136/gut.2007.144865]
- 48 **Potocnik U**, Ferkolj I, Glavac D, Dean M. Polymorphisms in multidrug resistance 1 (MDR1) gene are associated with refractory Crohn disease and ulcerative colitis. *Genes Immun* 2004; **5**: 530-539 [PMID: 15505619]
- 49 **Dotan I**. New serologic markers for inflammatory bowel disease diagnosis. *Dig Dis* 2010; **28**: 418-423 [PMID: 20926866 DOI: 10.1159/000320396]
- 50 **Rieder F**, Kugathasan S. Circulating antibodies against bacterial wall products: are there arguments for early immunosuppression? *Dig Dis* 2012; **30** Suppl 3: 55-66 [PMID: 23295693 DOI: 10.1159/000342603]
- 51 **Arnott ID**, Landers CJ, Nimmo EJ, Drummond HE, Smith BK, Targan SR, Satsangi J. Sero-reactivity to microbial components in Crohn's disease is associated with disease severity and progression, but not NOD2/CARD15 genotype. *Am J Gastroenterol* 2004; **99**: 2376-2384 [PMID: 15571586]
- 52 **Dubinsky MC**. What is the role of serological markers in the diagnosis of IBD? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S185-S186 [PMID: 18816787 DOI: 10.1002/ibd.20585]
- 53 **Dubinsky M**. What is the role of serological markers in IBD? Pediatric and adult data. *Dig Dis* 2009; **27**: 259-268 [PMID: 19786750 DOI: 10.1159/000228559]
- 54 **Fleshner PR**, Vasiliauskas EA, Kam LY, Fleshner NE, Gaiennie J, Abreu-Martin MT, Targan SR. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. *Gut* 2001; **49**: 671-677 [PMID: 11600470]
- 55 **Däbritz J**, Bonkowski E, Chalk C, Trapnell BC, Langhorst J, Denson LA, Foell D. Granulocyte macrophage colony-stimulating factor auto-antibodies and disease relapse in inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 1901-1910 [PMID: 24145675 DOI: 10.1038/ajg.2013.360]
- 56 **Bonneau J**, Dumestre-Perard C, Rinaudo-Gaujous M, Genin C, Sparrow M, Roblin X, Paul S. Systematic review: new serological markers (anti-glycan, anti-GP2, anti-GM-CSF Ab) in the prediction of IBD patient outcomes. *Autoimmun Rev* 2015; **14**: 231-245 [PMID: 25462578 DOI: 10.1016/j.autrev.2014.11.004]
- 57 **Paul S**, Boschetti G, Rinaudo-Gaujous M, Moreau A, Del Tedesco E, Bonneau J, Presles E, Mounsef F, Clavel L, Genin C, Flourié B, Phelip JM, Nancey S, Roblin X. Association of Anti-glycan Antibodies and Inflammatory Bowel Disease Course. *J Crohns Colitis* 2015; **9**: 445-451 [PMID: 25895876 DOI: 10.1093/ecco-jcc/jjv063]
- 58 **Brignola C**, Lanfranchi GA, Campieri M, Bazzocchi G, Devoto M, Boni P, Farruggia P, Veggetti S, Tragnone A. Importance of laboratory parameters in the evaluation of Crohn's disease activity. *J Clin Gastroenterol* 1986; **8**: 245-248 [PMID: 3734355]
- 59 **Brignola C**, Iannone P, Belloli C, De Simone G, Bassein L, Gionchetti P, Belluzzi A, Campieri M, Barbara L. Prediction of relapse in patients with Crohn's disease in remission: a simplified index using laboratory tests, enhanced by clinical characteristics. *Eur J Gastroenterol Hepatol* 1994; **6**: 955-961
- 60 **Boirivant M**, Leoni M, Taricotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. *J Clin Gastroenterol* 1988; **10**: 401-405 [PMID: 3418087]
- 61 **Consigny Y**, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 551-557 [PMID: 16804391]
- 62 **Kallel L**, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, Karoui S, Zouari B, Boubaker J, Kaabachi N, Filali A. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. *Eur J Gastroenterol Hepatol* 2010; **22**: 340-345 [PMID: 19581809 DOI: 10.1097/MEG.0b013e32832bab49]
- 63 **Kiss LS**, Papp M, Lovasz BD, Vegh Z, Golovics PA, Janka E, Varga E, Szathmari M, Lakatos PL. High-sensitivity C-reactive protein for identification of disease phenotype, active disease, and clinical relapses in Crohn's disease: a marker for patient classification? *Inflamm Bowel Dis* 2012; **18**: 1647-1654 [PMID: 22081542 DOI: 10.1002/ibd.21933]
- 64 **Henriksen M**, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH, Moum B. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008; **57**: 1518-1523 [PMID: 18566104 DOI: 10.1136/gut.2007.146357]
- 65 **D'Incà R**, Dal Pont E, Di Leo V, Benazzato L, Martinato M, Lamboglia F, Oliva L, Sturniolo GC. Can calprotectin predict relapse risk in inflammatory bowel disease? *Am J Gastroenterol* 2008; **103**: 2007-2014 [PMID: 18802997]
- 66 **Tibble JA**, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000; **119**: 15-22 [PMID: 10889150]
- 67 **Costa F**, Mumolo MG, Ceccarelli L, Bellini M, Romano MR, Sterpi C, Ricchiuti A, Marchi S, Bottai M. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut* 2005; **54**: 364-368 [PMID: 15710984]
- 68 **Gisbert JP**, Bermejo F, Pérez-Calle JL, Taxonera C, Vera I, McNicholl AG, Algaba A, López P, López-Palacios N, Calvo M, González-Lama Y, Carneros JA, Velasco M, Maté J. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009; **15**: 1190-1198 [PMID: 19291780 DOI: 10.1002/ibd.20933]
- 69 **García-Sánchez V**, Iglesias-Flores E, González R, Gisbert JP, Gallardo-Valverde JM, González-Galilea A, Naranjo-Rodríguez A, de Dios-Vega JF, Muntané J, Gómez-Camacho F. Does fecal calprotectin predict relapse in patients with Crohn's disease and ulcerative colitis? *J Crohns Colitis* 2010; **4**: 144-152 [PMID: 21122498 DOI: 10.1016/j.crohns.2009.09.008]
- 70 **Naismith GD**, Smith LA, Barry SJ, Munro JJ, Laird S, Rankin K, Morris AJ, Winter JW, Gaya DR. A prospective evaluation of the predictive value of faecal calprotectin in quiescent Crohn's disease. *J Crohns Colitis* 2014; **8**: 1022-1029 [PMID: 24566170 DOI: 10.1016/j.crohns.2014.01.029]
- 71 **Willot S**, Vermeire S, Ohresser M, Rutgeerts P, Paintaud G, Belaiche J, De Vos M, Van Gossum A, Franchimont D, Colombel JF, Watier H, Louis E. No association between C-reactive protein gene polymorphisms and decrease of C-reactive protein serum concentration after infliximab treatment in Crohn's disease. *Pharmacogenet Genomics* 2006; **16**: 37-42 [PMID: 16344720]
- 72 **Louis E**, Belaiche J, Van Kemske C, Schaaf N, Mahieu P, Mary JY. Soluble interleukin-2 receptor in Crohn's disease. Assessment of disease activity and prediction of relapse. *Dig Dis Sci* 1995; **40**: 1750-1756 [PMID: 7648975]

- 73 **Louis E**, Belaiche J, van Kemseke C, Franchimont D, de Groot D, Gueenen V, Mary JY. A high serum concentration of interleukin-6 is predictive of relapse in quiescent Crohn's disease. *Eur J Gastroenterol Hepatol* 1997; **9**: 939-944 [PMID: 9391781]
- 74 **Yamamoto T**, Umegae S, Kitagawa T, Matsumoto K. Systemic and local cytokine production in quiescent ulcerative colitis and its relationship to future relapse: a prospective pilot study. *Inflamm Bowel Dis* 2005; **11**: 589-596 [PMID: 15905707]
- 75 **García-Sánchez V**, González R, Iglesias-Flores E, Gisbert JP, Angel-Rey JM, Soto-Escribano P, Gálvez-Calderón C, Reyes-López A, Pérez-Jiménez F, de Dios-Vega JF, Muntané J, Gómez-Camacho F. Can systemic cytokines predict relapse of inflammatory bowel disease? *Hepato-gastroenterology* 2011; **57**: 524-530 [PMID: 20698221]
- 76 **Vogelsang H**. Do changes in intestinal permeability predict disease relapse in Crohn's disease? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S162-S163 [PMID: 18816766 DOI: 10.1002/ibd.20617]
- 77 **Wyatt J**, Vogelsang H, Hübl W, Waldhöer T, Lochs H. Intestinal permeability and the prediction of relapse in Crohn's disease. *Lancet* 1993; **341**: 1437-1439 [PMID: 8099141]
- 78 **Hilsden RJ**, Meddings JB, Hardin J, Gall DG, Sutherland LR. Intestinal permeability and postheparin plasma diamine oxidase activity in the prediction of Crohn's disease relapse. *Inflamm Bowel Dis* 1999; **5**: 85-91 [PMID: 10338376]
- 79 **D'Inca R**, Di Leo V, Corrao G, Martines D, D'Odorico A, Mestriner C, Venturi C, Longo G, Sturmiolo GC. Intestinal permeability test as a predictor of clinical course in Crohn's disease. *Am J Gastroenterol* 1999; **94**: 2956-2960 [PMID: 10520851]
- 80 **Arnott ID**, Kingstone K, Ghosh S. Abnormal intestinal permeability predicts relapse in inactive Crohn disease. *Scand J Gastroenterol* 2000; **35**: 1163-1169 [PMID: 11145287]
- 81 **Jørgensen J**, Ranløv PJ, Bjerrum PJ, Diemer H, Bisgaard K, Elsborg L. Is an increased intestinal permeability a valid predictor of relapse in Crohn disease? *Scand J Gastroenterol* 2001; **36**: 521-527 [PMID: 11346207]
- 82 **Allez M**, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol* 2002; **97**: 947-953 [PMID: 12003431]
- 83 **Allez M**, Lémann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. *World J Gastroenterol* 2010; **16**: 2626-2632 [PMID: 20518084 DOI: 10.3748/wjg.v16.i21.2626]
- 84 **Carbannel F**, Lavergne A, Lémann M, Bitoun A, Vallée P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39**: 1550-1557 [PMID: 8026269]
- 85 **Frosliè KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162]
- 86 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-468; quiz e10-e11 [PMID: 19818785 DOI: 10.1053/j.gastro.2009.09.056]
- 87 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53 [PMID: 15972298]
- 88 **Matsumoto T**, Kuroki F, Mizuno M, Nakamura S, Iida M. Application of magnifying chromoscopy for the assessment of severity in patients with mild to moderate ulcerative colitis. *Gastrointest Endosc* 1997; **46**: 400-405 [PMID: 9402112]
- 89 **Fujiya M**, Saitoh Y, Nomura M, Maemoto A, Fujiya K, Watari J, Ashida T, Ayabe T, Obara T, Kohgo Y. Minute findings by magnifying colonoscopy are useful for the evaluation of ulcerative colitis. *Gastrointest Endosc* 2002; **56**: 535-542 [PMID: 12297770]
- 90 **Watanabe C**, Sumioka M, Hiramoto T, Noda I, Oba S, Akagi M, Kitamoto M, Yamada H, Imagawa M. Magnifying colonoscopy used to predict disease relapse in patients with quiescent ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1663-1669 [PMID: 19504617 DOI: 10.1002/ibd.20949]
- 91 **Ando T**, Nishio Y, Watanabe O, Takahashi H, Maeda O, Ishiguro K, Ishikawa D, Ohmiya N, Niwa Y, Goto H. Value of colonoscopy for prediction of prognosis in patients with ulcerative colitis. *World J Gastroenterol* 2008; **14**: 2133-2138 [PMID: 18407585 DOI: 10.3748/wjg.14.2133]
- 92 **Jauregui-Amezaga A**, López-Cerón M, Aceituno M, Jimeno M, Rodríguez de Miguel C, Pinó-Donnay S, Zabalza M, Sans M, Ricart E, Ordás I, González-Suárez B, Cuatrecasas M, Llach J, Panés J, Pellise M. Accuracy of advanced endoscopy and fecal calprotectin for prediction of relapse in ulcerative colitis: a prospective study. *Inflamm Bowel Dis* 2014; **20**: 1187-1193 [PMID: 24874457 DOI: 10.1097/MIB.000000000000069]
- 93 **Kiesslich R**, Duckworth CA, Moussata D, Gloeckner A, Lim LG, Goetz M, Pritchard DM, Galle PR, Neurath MF, Watson AJ. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. *Gut* 2012; **61**: 1146-1153 [PMID: 22115910 DOI: 10.1136/gutjnl-2011-300695]
- 94 **Buda A**, Hatem G, Neumann H, D'Inca R, Mescoli C, Piselli P, Jackson J, Bruno M, Sturmiolo GC. Confocal laser endomicroscopy for prediction of disease relapse in ulcerative colitis: a pilot study. *J Crohns Colitis* 2014; **8**: 304-311 [PMID: 24094597 DOI: 10.1016/j.crohns.2013.09.005]
- 95 **Li CQ**, Liu J, Ji R, Li Z, Xie XJ, Li YQ. Use of confocal laser endomicroscopy to predict relapse of ulcerative colitis. *BMC Gastroenterol* 2014; **14**: 45 [PMID: 24618122 DOI: 10.1186/1471-230X-14-45]
- 96 **Misteli H**, Koh CE, Wang LM, Mortensen NJ, George B, Guy R. Myenteric plexitis at the proximal resection margin is a predictive marker for surgical recurrence of ileocaecal Crohn's disease. *Colorectal Dis* 2015; **17**: 304-310 [PMID: 25581299 DOI: 10.1111/codi.12896]
- 97 **Bressenot A**, Peyrin-Biroulet L. Histologic features predicting postoperative Crohn's disease recurrence. *Inflamm Bowel Dis* 2015; **21**: 468-475 [PMID: 25437814 DOI: 10.1097/MIB.0000000000000224]
- 98 **Geboes K**, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000; **47**: 404-409 [PMID: 10940279]
- 99 **Bessisow T**, Lemmens B, Ferrante M, Bisschops R, Van Steen K, Geboes K, Van Assche G, Vermeire S, Rutgeerts P, De Hertogh G. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. *Am J Gastroenterol* 2012; **107**: 1684-1692 [PMID: 23147523 DOI: 10.1038/ajg.2012.301]
- 100 **Popp C**, Stăniceanu F, Micu G, Nichita L, Cioplea M, Mateescu RB, Voiosu T, Sticlaru L. Evaluation of histologic features with potential prognostic value in ulcerative colitis. *Rom J Intern Med* 2014; **52**: 256-262 [PMID: 25726628]
- 101 **Sipponen T**, Kolho KL. Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease. *Scand J Gastroenterol* 2015; **50**: 74-80 [PMID: 25523558 DOI: 10.3109/00365521.2014.987809]
- 102 **Lehmann FS**, Burri E, Beglinger C. The role and utility of faecal markers in inflammatory bowel disease. *Therap Adv Gastroenterol* 2015; **8**: 23-36 [PMID: 25553077 DOI: 10.1177/1756283X14553384]
- 103 **Roseth AG**, Fagerhol MK, Aadland E, Schjønby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992; **27**: 793-798 [PMID: 1411288]
- 104 **Fagerhol MK**, Dale I, Andersson T. A radioimmunoassay for a granulocyte protein as a marker in studies on the turnover of such cells. *Bull Eur Physiopathol Respir* 1980; **16** Suppl: 273-282 [PMID: 7225633]
- 105 **Costa F**, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, Sterpi C, Marchi S, Maltinti G. Role of faecal calprotectin

- as non-invasive marker of intestinal inflammation. *Dig Liver Dis* 2003; **35**: 642-647 [PMID: 14563186]
- 106 **Thjodleifsson B**, Sigthorsson G, Cariglia N, Reynisdottir I, Gudbjartsson DF, Kristjansson K, Meddings JB, Gudnason V, Wandall JH, Andersen LP, Sherwood R, Kjeld M, Oddsson E, Gudjonsson H, Bjarnason I. Subclinical intestinal inflammation: an inherited abnormality in Crohn's disease relatives? *Gastroenterology* 2003; **124**: 1728-1737 [PMID: 12806605]
 - 107 **Walkiewicz D**, Werlin SL, Fish D, Scanlon M, Hanaway P, Kugathasan S. Fecal calprotectin is useful in predicting disease relapse in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 669-673 [PMID: 18240279 DOI: 10.1002/ibd.20376]
 - 108 **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70. e5; quiz e31 [PMID: 21945953 DOI: 10.1053/j.gastro.2011.09.034]
 - 109 **Mao R**, Xiao YL, Gao X, Chen BL, He Y, Yang L, Hu PJ, Chen MH. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2012; **18**: 1894-1899 [PMID: 22238138 DOI: 10.1002/ibd.22861]
 - 110 **Yamamoto T**, Shiraki M, Bamba T, Umegae S, Matsumoto K. Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. *Int J Colorectal Dis* 2014; **29**: 485-491 [PMID: 24343276 DOI: 10.1007/s00384-013-1817-3]
 - 111 **Scaioi E**, Scagliarini M, Cardamone C, Liverani E, Ugolini G, Festi D, Bazzoli F, Belluzzi A. Clinical application of faecal calprotectin in ulcerative colitis patients. *Eur J Gastroenterol Hepatol* 2015; **27**: 1418-1424 [PMID: 26308711 DOI: 10.1097/MEG.0000000000000461]
 - 112 **Ferreiro-Iglesias R**, Barreiro-de Acosta M, Otero Santiago M, Lorenzo Gonzalez A, Alonso de la Peña C, Benitez Estevez AJ, Dominguez-Muñoz JE. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. *J Clin Gastroenterol* 2015; Epub ahead of print [PMID: 25811118]
 - 113 **Molander P**, af Björkesten CG, Mustonen H, Haapamäki J, Vauhkonen M, Kolho KL, Färkkilä M, Sipponen T. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNF α blocking agents. *Inflamm Bowel Dis* 2012; **18**: 2011-2017 [PMID: 22223566 DOI: 10.1002/ibd.22863]
 - 114 **De Vos M**, Louis EJ, Jahnsen J, Vandervoort JG, Noman M, Dewit O, D'haens GR, Franchimont D, Baert FJ, Torp RA, Henriksen M, Potvin PM, Van Hootegeem PP, Hindryckx PM, Moreels TG, Collard A, Karlsen LN, Kittang E, Lambrecht G, Grimstad T, Koch J, Lygren I, Coche JC, Mana F, Van Gossun A, Belaiche J, Cool MR, Fontaine F, Maisin JM, Muls V, Neuville B, Staessen DA, Van Assche GA, de Lange T, Solberg IC, Vander Cruyssen BJ, Vermeire SA. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. *Inflamm Bowel Dis* 2013; **19**: 2111-2117 [PMID: 23883959 DOI: 10.1097/MIB.0b013e31829b2a37]
 - 115 **Tibble J**, Teahon K, Thjodleifsson B, Roseth A, Sigthorsson G, Bridger S, Foster R, Sherwood R, Fagerhol M, Bjarnason I. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000; **47**: 506-513 [PMID: 10986210]
 - 116 **Moum B**, Jahnsen J, Bernklev T. Fecal calprotectin variability in Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 1091-1092 [PMID: 19834972 DOI: 10.1002/ibd.21136]
 - 117 **Calafat M**, Cabré E, Mañosa M, Lobatón T, Marín L, Domènech E. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling? *Inflamm Bowel Dis* 2015; **21**: 1072-1076 [PMID: 25793326 DOI: 10.1097/MIB.0000000000000349]
 - 118 **Lasson A**, Stotzer PO, Öhman L, Isaksson S, Sapanara M, Strid H. The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis. *J Crohns Colitis* 2015; **9**: 26-32 [PMID: 25008478 DOI: 10.1016/j.crohns.2014.06.002]
 - 119 **Buderus S**, Boone J, Lyerly D, Lentze MJ. Fecal lactoferrin: a new parameter to monitor infliximab therapy. *Dig Dis Sci* 2004; **49**: 1036-1039 [PMID: 15309897]
 - 120 **Sugi K**, Saitoh O, Hirata I, Katsu K. Fecal lactoferrin as a marker for disease activity in inflammatory bowel disease: comparison with other neutrophil-derived proteins. *Am J Gastroenterol* 1996; **91**: 927-934 [PMID: 8633583]
 - 121 **Angriman I**, Scarpa M, D'Inca R, Basso D, Ruffolo C, Polese L, Sturniolo GC, D'Amico DF, Plebani M. Enzymes in feces: useful markers of chronic inflammatory bowel disease. *Clin Chim Acta* 2007; **381**: 63-68 [PMID: 17368600]
 - 122 **Walker TR**, Land ML, Kartashov A, Saslowsky TM, Lyerly DM, Boone JH, Rufo PA. Fecal lactoferrin is a sensitive and specific marker of disease activity in children and young adults with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 414-422 [PMID: 17414136]
 - 123 **Sipponen T**, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J Gastroenterol* 2010; **45**: 325-331 [PMID: 20034360 DOI: 10.3109/00365520903483650]
 - 124 **Foell D**, Wittkowski H, Ren Z, Turton J, Pang G, Daebritz J, Ehrchen J, Heidemann J, Borody T, Roth J, Clancy R. Phagocyte-specific S100 proteins are released from affected mucosa and promote immune responses during inflammatory bowel disease. *J Pathol* 2008; **216**: 183-192 [PMID: 18729068 DOI: 10.1002/path.2394]
 - 125 **Kaiser T**, Langhorst J, Wittkowski H, Becker K, Friedrich AW, Rueffer A, Dobos GJ, Roth J, Foell D. Faecal S100A12 as a non-invasive marker distinguishing inflammatory bowel disease from irritable bowel syndrome. *Gut* 2007; **56**: 1706-1713 [PMID: 17675327]
 - 126 **Sidler MA**, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. *Inflamm Bowel Dis* 2008; **14**: 359-366 [PMID: 18050298]
 - 127 **Däbritz J**, Langhorst J, Lügering A, Heidemann J, Mohr M, Wittkowski H, Krummenerl T, Foell D. Improving relapse prediction in inflammatory bowel disease by neutrophil-derived S100A12. *Inflamm Bowel Dis* 2013; **19**: 1130-1138 [PMID: 23377171 DOI: 10.1097/MIB.0b013e318280blcd]
 - 128 **Peyrin-Biroulet L**, Loftus EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; **105**: 289-297 [PMID: 19861953 DOI: 10.1038/ajg.2009.579]
 - 129 **Yamamoto T**, Keighley MR. Smoking and disease recurrence after operation for Crohn's disease. *Br J Surg* 2000; **87**: 398-404 [PMID: 10759731]
 - 130 **Spinelli A**, Sacchi M, Fiorino G, Danese S, Montorsi M. Risk of postoperative recurrence and postoperative management of Crohn's disease. *World J Gastroenterol* 2011; **17**: 3213-3219 [PMID: 21912470 DOI: 10.3748/wjg.v17.i27.3213]
 - 131 **Van Assche G**, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63-101 [PMID: 21122490 DOI: 10.1016/j.crohns.2009.09.009]
 - 132 **Buisson A**, Chevaux JB, Bommelaer G, Peyrin-Biroulet L. Diagnosis, prevention and treatment of postoperative Crohn's disease recurrence. *Dig Liver Dis* 2012; **44**: 453-460 [PMID: 22265329 DOI: 10.1016/j.dld.2011.12.018]
 - 133 **Lamb CA**, Mohiuddin MK, Gicquel J, Neely D, Bergin FG, Hanson JM, Mansfield JC. Faecal calprotectin or lactoferrin can

- identify postoperative recurrence in Crohn's disease. *Br J Surg* 2009; **96**: 663-674 [PMID: 19384912 DOI: 10.1002/bjs.6593]
- 134 **Orlando A**, Modesto I, Castiglione F, Scala L, Scimeca D, Rispo A, Teresi S, Mocciano F, Criscuoli V, Marrone C, Platania P, De Falco T, Maisano S, Nicoli N, Cottone M. The role of calprotectin in predicting endoscopic post-surgical recurrence in asymptomatic Crohn's disease: a comparison with ultrasound. *Eur Rev Med Pharmacol Sci* 2006; **10**: 17-22 [PMID: 16494106]
- 135 **Qiu Y**, Mao R, Chen BL, He Y, Zeng ZR, Xue L, Song XM, Li ZP, Chen MH. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2015; **21**: 315-322 [PMID: 25569739 DOI: 10.1097/MIB.0000000000000262]
- 136 **Wright EK**, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, Leach S, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Jakobovits SL, Florin TH, Gibson PR, Debinski H, Macrae FA, Samuel D, Kronborg I, Radford-Smith G, Selby W, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Day AS, Desmond PV, Garry RB. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology* 2015; **148**: 938-947.e1 [PMID: 25620670 DOI: 10.1053/j.gastro.2015.01.026]

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