



ELSEVIER

available at [www.sciencedirect.com](http://www.sciencedirect.com)



SPECIAL ARTICLE

# The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis

Gert Van Assche<sup>\*,1</sup>, Axel Dignass<sup>\*,1</sup>, Julian Panes, Laurent Beaugerie, John Karagiannis, Mathieu Allez, Thomas Ochsenkühn, Tim Orchard, Gerhard Rogler, Edouard Louis, Limas Kupcinkas, Gerassimos Mantzaris, Simon Travis, Eduard Stange  
for the European Crohn's and Colitis Organisation (ECCO)

Received 11 September 2009; received in revised form 7 December 2009; accepted 7 December 2009

**KEYWORDS**

Crohn's disease;  
Definitions;  
Diagnosis;  
Investigations;  
Histopathology;  
Classification;  
Activity indices

**Contents**

1. Introduction . . . . .	8
1.1. Definitions . . . . .	9
1.1.1. Active disease . . . . .	9
1.1.2. Remission . . . . .	9
1.1.3. Response . . . . .	10
1.1.4. Relapse . . . . .	10
1.1.5. Early relapse . . . . .	10
1.1.6. Pattern of relapse . . . . .	11
1.1.7. Steroid-refractory disease . . . . .	11
1.1.8. Steroid-dependent disease . . . . .	11
1.1.9. Recurrence . . . . .	11

\* Corresponding authors. Van Assche is to be contacted at Division of Gastroenterology, Leuven University Hospitals, 49 Herestraat, BE 3000 Leuven, Belgium. Tel.: +32 16 34 42 25; fax: +32 16 34 44 19. Dignass, Department of Medicine I, Markus-Krankenhaus Wilhelm-Epstein-Str. 2, D-60431 Frankfurt/Main, Germany. Tel.: +49 69 9533 2201; fax: +49 69 9533 2291.

*E-mail addresses:* [Gert.vanassche@uzleuven.be](mailto:Gert.vanassche@uzleuven.be) (G. Van Assche), [axel.dignass@fdk.info](mailto:axel.dignass@fdk.info) (A. Dignass).

<sup>1</sup> These authors acted as convenors of the Consensus and contributed equally to this paper.

1.1.10. Morphologic recurrence . . . . .	11
1.1.11. Clinical recurrence . . . . .	11
1.1.12. Localised disease . . . . .	11
1.1.13. Extensive Crohn's disease . . . . .	11
1.1.14. New patient . . . . .	11
1.1.15. Alternative therapy . . . . .	11
1.1.16. Complementary therapies . . . . .	11
1.1.17. Expert opinion . . . . .	11
2. Clinical diagnosis and imaging . . . . .	11
2.1. Clinical features of CD . . . . .	12
2.2. Diagnosis . . . . .	12
2.2.1. History and examination . . . . .	12
2.2.2. Initial laboratory investigations . . . . .	13
2.2.3. Procedures recommended to establish the diagnosis . . . . .	13
2.3. Extent of disease . . . . .	14
2.3.1. Procedures recommended for establishing the extent of CD . . . . .	14
2.3.2. Procedures recommended for establishing the extent of stricturing CD . . . . .	14
2.3.3. Procedures recommended for detecting extramural complications . . . . .	15
2.3.4. Role of gastroduodenoscopy and biopsy in a patient with CD . . . . .	15
2.3.5. Role of small bowel capsule endoscopy (SBCE) and double balloon enteroscopy (DBE) in suspected or proven CD . . . . .	15
2.3.6. Procedures recommended preoperatively . . . . .	16
3. The histological diagnosis of Crohn's disease . . . . .	16
3.1. Procedures for the diagnosis with endoscopic biopsies . . . . .	16
3.1.1. Number of biopsies . . . . .	16
3.1.2. Handling of biopsies . . . . .	16
3.2. Diagnostic features . . . . .	17
3.2.1. Combined microscopic features . . . . .	17
3.2.2. Focal or patchy inflammation . . . . .	17
3.2.3. Crypt irregularity . . . . .	17
3.2.4. Granulomas . . . . .	17
3.2.5. Number of features needed for diagnosis . . . . .	17
3.3. Histology and dysplasia–intraepithelial neoplasia . . . . .	18
3.3.1. Number of biopsies . . . . .	19
3.3.2. Microscopic features . . . . .	19
3.3.3. Additional techniques . . . . .	19
3.4. Surgery and pathology . . . . .	19
3.5. Histology and disease activity . . . . .	19
4. Classification of Crohn's disease . . . . .	20
4.1. General recommendations . . . . .	20
4.2. Specific components . . . . .	21
4.2.1. Montréal phenotype classification . . . . .	21
4.2.2. Clinical predictors at diagnosis of subsequent phenotype . . . . .	21
4.2.3. Classification by serum CRP and faecal markers . . . . .	21
4.2.4. Correlation between genetic and serological markers and phenotype . . . . .	21
4.2.5. Need for a composite predictive index at diagnosis . . . . .	22
Contributors . . . . .	22
Acknowledgements . . . . .	22
References . . . . .	22

## 1. Introduction

Crohn's disease is a lifelong disease arising from an interaction between genetic and environmental factors, but observed predominantly in developed countries of the world. The precise aetiology is unknown and therefore a causal therapy is not yet available. Within Europe there is a distinct North–South gradient, but the incidence appears to have increased in Southern countries in recent years.<sup>1</sup> Many patients live with a considerable symptom

burden despite medical treatment in the hope that the aetiology of the disease will shortly be revealed and curative therapies emerge. Since it is uncertain that the precise pathogenesis of Crohn's disease will be revealed anytime soon, clinicians have to advise patients on the basis of information available today rather than an unknown future. Despite a multiplicity of randomised trials there will always be many questions that can only be answered by the exercise of judgement and opinion. This leads to differences in practice between clinicians, which

may be brought into sharp relief by differences in emphasis between countries.

The Consensus endeavours to address these differences. The Consensus is not meant to supersede the guidelines of different countries (such as those from the UK,<sup>2</sup> Germany,<sup>3</sup> or France), which reach broadly the same conclusions since they are, after all, based on the same evidence. Rather, the aim of the Consensus is to promote a European perspective on the management of Crohn's disease and its dilemmas. Since the development of guidelines is an expensive and time-consuming process, it may help to avoid duplication of effort in the future. A Consensus is also considered important because an increasing number of therapeutic trials are based in Europe, especially in eastern European countries where practice guidelines have yet to be published.

This document is based on the European consensus on the diagnosis and management of Crohn's disease, reached by the European Crohn's and Colitis Organisation (ECCO) at a meeting held in Prague on 24th September 2004.<sup>4,5</sup> On 18th October 2008, in Vienna, the guidelines were revised at a meeting of the ECCO guidelines task force. ECCO is a forum for specialists in inflammatory bowel disease from 32 European countries. It was established in 2000 with the common purpose of promoting European views, clinical trials and specialist training in inflammatory bowel disease. The Consensus is grouped into three parts: definitions and diagnosis; current management; and management of special situations. This first section concerns aims and methods of the Consensus, as well as diagnosis, pathology, and classification of Crohn's disease. The second section on Current Management includes treatment of active disease, maintenance of medically-induced remission and surgery of Crohn's disease. The third section on Special Situations in Crohn's disease includes post-operative recurrence, fistulating disease, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations and alternative therapy.

The strategy to reach the Consensus on the guideline revisions involved six steps:

- Guideline statements of 2004 were analysed systematically by the chairs of the working parties. Guideline statements selected for change and questions unresolved by the 2004 ECCO guidelines were distributed to the working party members. Participants were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure).<sup>6</sup>
- In parallel, the working parties performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level (EL) was graded (Table 1.1) according to the Oxford Centre for Evidence-Based Medicine.<sup>7</sup>
- Provisional guideline statements on their topic were then written by the chairmen, posted on a weblog. Discussions and exchange of the literature evidence among the working party members was then performed on the weblog. This process was supervised by Axel Dignass and Gert Van Assche.
- On September 30 all working party chairs submitted the proposed changes to the 2004 guidelines to Gert Van Assche and Axel Dignass, who compiled them in a working document.
- The working parties then met in Vienna on the 18th October 2008 to agree on the statements. Technically this was done by projecting the statements and revising them on screen until a consensus was reached. Consensus was defined as agreement by >80% of participants, termed a Consensus Statement and numbered for convenience in the document. Each recommendation was graded (RG) according to the Oxford Centre for Evidence Based Medicine,<sup>7</sup> based on the level of evidence (Table 1.1).
- The final document on each topic was written by the chairmen in conjunction with their working party. Consensus guideline statements in bold are followed by comments on the evidence and opinion. Statements are intended to be read in context with qualifying comments and not read in isolation. The final text was edited for consistency of style by A. Dignass, J Lindsay, SPL Travis and G Van Assche before being circulated and approved by the participants. In some areas the level of evidence is generally low, which reflects the paucity of randomised controlled trials. Consequently expert opinion is included where appropriate.

## 1.1. Definitions

Common agreement was reached about frequently used terms. While the significance of some terms (such as 'early-' or 'pattern of relapse') is undetermined, such terms reflect clinical decision making (such as when to start immunomodulators). The arbitrariness of some of the definitions is recognized, but the Consensus considers it useful to agree to the terminology.

### 1.1.1. Active disease

For the purposes of this Consensus, clinical disease activity is grouped into mild, moderate and severe (Table 1.2). These are not precisely defined entities. Most clinical trials in patients with active Crohn's disease recruit patients with a Crohn's Disease Activity Index (CDAI) of >220. The fallibility of this threshold is illustrated by the high placebo response in recent trials of biological therapy<sup>8</sup> and the trend is now to use a CRP of >10 mg/L in conjunction with the CDAI. Remission (see below) is widely accepted as a CDAI of <150 and response is increasingly defined as a decrease in CDAI by  $\geq 100$  points. It would make sense to define disease activity in groups of 100 points, at least until a sensitive, responsive and validated index superior to the CDAI is developed.<sup>9</sup> This is an inconsistency that needs to be resolved, but until it can be modeled on clinical trial data sets disease activity is generally graded as in Table 1.2.

### 1.1.2. Remission

The criterion used in the majority of clinical trials when selecting Crohn's disease patients in clinical remission is a CDAI of <150.<sup>10</sup> This has become the customary definition and is accepted for the purposes of evaluating the literature and clinical trials for as long as the CDAI remains the principal index for evaluating outcome in trials of Crohn's disease. In several studies, a biological index of Brignola of <100<sup>11,12</sup> was also a requirement. This has the advantage of objectivity, but is not used in clinical practice. In keeping with the views of the International Organisation for the study of Inflammatory Bowel Disease, ECCO believes that studies

**Table 1.1** Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine. For details see [http://www.cebm.net/levels\\_of\\_evidence.asp#refs](http://www.cebm.net/levels_of_evidence.asp#refs).

Level	Individual study	Technique
1a	Systematic review (SR) with homogeneity of Level 1 diagnostic studies	Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort study with good reference standards	Individual RCT (with narrow Confidence Interval)
1c	Specificity is so high that a positive result rules in the diagnosis ("SpPin") or sensitivity is so high that a negative result rules out the diagnosis ("SnNout")	All or none
2a	SR with homogeneity of level >2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; e.g., <80% follow up)
2c		"Outcomes" research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case-control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual case-control study
4	Case-control study, poor or non-independent reference standard	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of recommendation		
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies	
C	Level 4 studies or extrapolations from level 2 or 3 studies	
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	

evaluating the maintenance of remission in Crohn's disease should last at least 12 months.<sup>5,10</sup>

### 1.1.3. Response

Response should be defined by a  $\Delta$ CDAI of  $\geq -100$  points, although in some studies, including those initially evaluating the effectiveness of infliximab, a lesser end point of response with a reduction in CDAI by  $\geq 70$  points<sup>13,14</sup> was used.

### 1.1.4. Relapse

The term relapse is used to define a flare of symptoms in a patient with established CD who is in clinical remission, either spontaneously or after medical treatment. Relapse is preferably confirmed by laboratory parameters, imaging or endoscopy in clinical practice. For the purposes of clinical

trials a CDAI of  $>150$  with an increase of more than 70 points has been proposed.<sup>10</sup> However, if a therapeutic response is defined as a decrease in CDAI by  $\geq 100$  points, then the definition would more rationally be a CDAI of  $>150$  with an increase of 100 points from baseline. There is no international agreement on this, but future trials on Crohn's disease should take this into account. Other definitions (including CDAI  $>150$ , or a CDAI  $>250$ , or an increase of 50 points if the baseline was between 150 and 250) are considered less acceptable.

### 1.1.5. Early relapse

An arbitrary, but clinically relevant period of  $<3$  months after achieving remission on previous therapy defines early relapse. The therapeutic significance needs to be defined.

**Table 1.2** Grading of disease activity in Crohn's disease.

Mild	Moderate	Severe
Equivalent to a CDAI of 150–220 e.g. Ambulatory, eating and drinking, $<10\%$ weight loss. No features of obstruction, fever, dehydration, abdominal mass, or tenderness. CRP usually increased above the upper limit of normal.	Equivalent to a CDAI of 220–450 e.g. Intermittent vomiting, or weight loss $>10\%$ . Treatment for mild disease ineffective, or tender mass. No overt obstruction. CRP elevated above the upper limit of normal.	Equivalent to a CDAI of $>450$ e.g. Cachexia (BMI $<18 \text{ kg m}^{-2}$ ), or evidence of obstruction or abscess. Persistent symptoms despite intensive treatment. CRP increased.

Note: symptoms of obstruction are not always related to inflammatory activity and should be investigated with additional imaging as outlined further in the paper.

**1.1.6. Pattern of relapse**

Relapse may be infrequent ( $\leq 1/\text{yr}$ ), frequent ( $\geq 2$  relapses/yr), or continuous (persistent symptoms of active CD without a period of remission). Although the terms are arbitrary, they are considered clinically relevant. The prognostic significance needs to be determined.

The term 'chronic active disease' has been used in the past to define a patient who is dependent on, refractory to, or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions are preferred, including steroid-refractory or steroid-dependence.

**1.1.7. Steroid-refractory disease**

Patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks.

**1.1.8. Steroid-dependent disease**

Patients who are either

- i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting steroids, without recurrent active disease, or
- ii) who have a relapse within 3 months of stopping steroids.

The assessment of steroid-refractoriness or -dependence should be made after careful exclusion of disease-specific complications.

This definition of steroid-dependence requires that the total duration of steroids does not exceed 3 months before a threshold equivalent to prednisolone 10 mg/day is reached. Patients are still considered steroid-dependent if they relapse within 3 months of stopping steroids. Although these limits are arbitrary, they serve as guidance for clinical practice and may be used for uniformity in clinical trials. The aim should be to withdraw steroids completely.

**1.1.9. Recurrence**

The term recurrence is best used to define the reappearance of lesions after surgical resection (while relapse refers to the reappearance of symptoms, above).

**1.1.10. Morphologic recurrence**

The appearance of new CD lesions after complete resection of macroscopic disease, usually in the neo-terminal ileum and/or at the anastomosis, detected by endoscopy, radiology or surgery.<sup>15,16</sup> *Endoscopic recurrence* is currently evaluated and graded according to the criteria of Rutgeerts et al. (0: no lesions; 1: less than 5 aphthous lesions; 2: more than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolonic anastomotic lining (<1 cm); 3: diffuse aphthous ileitis with diffusely inflamed mucosa; and 4: diffuse ileal inflammation with larger ulcers, nodules, or narrowing. Hyperaemia and oedema alone are not considered as signs of recurrence).<sup>15</sup> Also, all post-operative changes visualized by ultrasound or CT/MRI are not specifically indicating disease recurrence (also see Section 2.3.1).

**1.1.11. Clinical recurrence**

The appearance of CD symptoms after complete resection of macroscopic disease, provided (for the purposes of clinical trials) that recurrence of lesions is confirmed.<sup>16</sup> Symptoms suggestive of CD can be caused by motility disturbances or bile malabsorption, which underscores the need for confirmation of inflammatory, penetrating or fibrotic lesions.<sup>17</sup>

**1.1.12. Localised disease**

Intestinal Crohn's disease affecting <30 cm in extent. This usually applies to an ileocaecal location (<30 cm ileum  $\pm$  right colon), but could apply to isolated colonic disease, or conceivably to proximal small intestinal disease.

**1.1.13. Extensive Crohn's disease**

Intestinal Crohn's disease affecting >100 cm in extent whatever the location. This applies to the sum of inflammation in discontinuous segments. While there is clearly a 'grey area' of disease extent (between 30 and 100 cm) and the length is arbitrary, this definition of extensive disease recognises the greater inflammatory burden and implications for medical and surgical decision making with this extent of disease.

**1.1.14. New patient**

A patient with active CD presenting at, or shortly after diagnosis, with no previous therapy for CD.

**1.1.15. Alternative therapy**

One that is used in place of conventional medicine.

**1.1.16. Complementary therapies**

Similar treatments used alongside conventional medicine (see Section 1.1.15 for comment).

**1.1.17. Expert opinion**

The term 'expert' is used here to refer to the opinion of the specialists in inflammatory bowel disease representing multiple disciplines from 22 European countries who contributed to the ECCO Consensus. In some sections opinions from individual members of other expert bodies were obtained, including individuals of the European Society of Pathology (ESP) working group on Digestive Diseases, or the European Society of Gastrointestinal and Abdominal Radiology (ESGAR).

**2. Clinical diagnosis and imaging**

Principal changes with respect to the 2004 ECCO guidelines.

- MR or CT enterography/enteroclysis is an imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement of CD including extramural complications [statements 2F and 2G].
- Small bowel capsule endoscopy should be reserved for those patients with a high clinical suspicion of CD despite negative investigation by ileocolonoscopy and other imaging techniques [statement 2I].

CD most frequently presents in late adolescence or early adulthood and is equally distributed between the sexes.<sup>18</sup>

Symptoms at presentation vary depending on the location, behaviour and severity of disease, as well as extraintestinal manifestations and medication. The aim is to establish the diagnosis and distribution of disease by appropriate techniques, because this influences the choice of treatment. Both gastroenterologists and radiologists have been involved in the development of the guidance on appropriate radiological techniques for patients with CD.

## 2.1. Clinical features of CD

### **ECCO statement 2A**

**Symptoms of CD are heterogeneous, but commonly include diarrhoea for more than 6 weeks, abdominal pain and/or weight loss. These symptoms should raise the suspicion of CD, especially in patients at a young age. Systemic symptoms of malaise, anorexia, or fever are common [EL5, RG D].**

Chronic diarrhoea is the most common presenting symptom<sup>19</sup> a definition of a decrease in faecal consistency for more than 6 weeks may be adequate to differentiate this from self limited, infectious diarrhoea.<sup>20</sup> More acute presentations may occur, and acute terminal ileal Crohn's disease may be mistaken for acute appendicitis. Chronic non-specific symptoms mimicking irritable bowel syndrome (IBS), unexplained anaemia and growth failure in children should also be considered to avoid delayed diagnosis.<sup>21,22</sup> Abdominal pain and weight loss are seen in about 70% and 60% respectively of patients before diagnosis. Although the irritable bowel syndrome is more common than CD, associated systemic symptoms, blood in stools and weight loss, should always trigger further investigations. Blood and/or mucus in the stool may be seen in up to 40% to 50% of patients with Crohn's colitis, but less frequently than in ulcerative colitis (UC).<sup>23</sup> Patients may present with extraintestinal manifestations of Crohn's disease before the gastrointestinal symptoms become prominent. Abnormalities of the musculoskeletal system are the most common extraintestinal manifestations of IBD, encompassing peripheral and axial joints.<sup>24</sup> Extraintestinal manifestations are most common when CD affects the colon. Perianal fistulas are present in 10% of patients at the time of diagnosis,<sup>25</sup> and may be the presenting complaint.

## 2.2. Diagnosis

### **ECCO statement 2B**

**A single gold standard for the diagnosis of CD is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Genetic testing is currently not recommended for routine diagnosis or management of CD. [EL5, RG D].**

CD is a heterogeneous entity comprising a variety of complex phenotypes in terms of age of onset, disease location and disease behaviour.<sup>26</sup> As there is no single way to diagnose CD, Lennard-Jones et al. have defined macroscopic and microscopic criteria to establish the diagnosis. The macroscopic diagnostic tools include physical examination, endoscopy, radiology, and examination of an operative specimen. Microscopic features can be only partly assessed on mucosal biopsy, but completely assessed on an operative specimen. The diagnosis depends on the finding of discontinuous and often granulomatous intestinal inflammation.<sup>23</sup> The current view is that the diagnosis is established by a non-strictly defined combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings and, more recently, serology. This still results in diagnostic obstacles. A change in diagnosis to UC during the first year occurs in about 5% of cases. IBD restricted to the colon that cannot be allocated to the CD or UC category is best termed colitis unclassified and the term indeterminate colitis confined to operative specimens as originally described.<sup>27</sup> The indiscriminate use of the term indeterminate colitis to cover all cases of diagnostic uncertainty is confusing in the literature and imprecise in practice.

### 2.2.1. History and examination

#### **ECCO statement 2C**

**A full history should include detailed questioning about the onset of symptoms, recent travel, food intolerances, medication (including antibiotics and non-steroidal anti-inflammatory drugs), and history of appendectomy [EL5, RG D]. Particular attention should be paid to well proven risk factors including smoking, family history, and recent infectious gastroenteritis [EL1b RGB].**

#### **ECCO statement 2D**

**Careful questioning about nocturnal symptoms, features of extraintestinal manifestations involving the mouth, skin, eye, or joints, episodes of perianal abscess, or anal fissure is appropriate. General examination includes general well-being, pulse rate, blood pressure, temperature, abdominal tenderness or distension, palpable masses, perineal and oral inspection, and rectal digital examination. Measurement of body weight and calculation of body mass index are recommended [EL5, RG D].**

Smoking, prior appendectomy, and a family history of IBD have been reproduced as risk factors for the onset of CD.<sup>28,29</sup> Infectious gastroenteritis is followed by an increased

risk (four-fold) of developing CD especially in the following year, although the absolute risk is low.<sup>30</sup> Retrospective studies on non-steroidal anti-inflammatory drugs as a risk factor for CD are less consistent.<sup>31</sup>

### 2.2.2. Initial laboratory investigations

#### ECCO statement 2E

Check for signs of acute and/or chronic inflammatory response, anaemia, fluid depletion, and signs of malnutrition or malabsorption [EL5, RG D]. Initial laboratory investigations should include CRP [EL2, RG B], and full blood count [EL5, RG D]. If C-reactive protein is not available, then measurement of the erythrocyte sedimentation rate (ESR) may be used [EL5, RG D]. Other biochemical markers may also be used to identify gut inflammation, in particular faecal calprotectin. [EL1b RG B] Microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin is recommended [EL2, RG B]. Additional stool tests may be needed for patients who have travelled abroad [EL5, RG D].

Anaemia and thrombocytosis represent the most common changes in the full blood count of patients with CD. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are standard laboratory surrogates of the acute phase response to inflammation. The CRP broadly correlates with disease activity of CD assessed by standard indices and indicates serial changes in inflammatory activity because of its short half life of 19 h.<sup>29,32–34</sup> The ESR less accurately measures intestinal inflammation in CD by reflecting changes of plasma protein concentration and packed cell volume. The ESR increases with disease activity, but correlates better with colonic rather than ileal disease.<sup>35</sup> Estimation of faecal markers of inflammation have been shown to correlate well with intestinal inflammation, particularly faecal calprotectin, which has a positive predictive value of 85–90% in distinguishing IBD from irritable bowel syndrome<sup>36–40</sup> and lactoferrin.<sup>36,40</sup> However, while these markers have been tested in relatively small populations as diagnostic markers, most evidence comes from studies performed on patients with CD predicting *relapse* rather than in initial *diagnosis*. Improved diagnostic accuracy may come from newer tests including faecal S100A12.<sup>41,42</sup> None of the above parameters is specific enough to permit differentiation from UC or enteric infection. Evidence for a pathophysiological role of certain strains of luminal bacteria in genetically susceptible hosts in CD comes from animal models and studies on innate immunity. None yet have a diagnostic role. The value of routine stool examination in patients with suspected CD or exacerbations of disease arises from both the differential diagnosis and high concordance with enteric infections such as *C. difficile*.<sup>43</sup>

Serologic testing currently available may be used as an adjunct to diagnosis, but the accuracy of the best of the available tests (ASCA and ANCA) is such that they are unlikely to be useful in routine diagnosis, and are ineffective at differentiating colonic Crohn's disease from ulcerative colitis.<sup>44,45</sup> Other serological markers such as anti-OmpC and CBir1 have not yet been shown to help in differentiating CD from UC.<sup>34,46–48</sup> Despite the advances in the field of Crohn's disease genetics there are currently no genetic tests which are recommended routinely for diagnosis.

### 2.2.3. Procedures recommended to establish the diagnosis

#### ECCO statement 2F

For suspected CD, ileocolonoscopy and biopsies from the terminal ileum as well as each colonic segment to look for microscopic evidence of CD are first line procedures to establish the diagnosis [EL1b, RG A]. Irrespective of the findings at ileocolonoscopy, further investigation is recommended to examine the location and extent of any CD in the upper gastrointestinal tract or small bowel [EL5, RG D].

Colonoscopy with multiple biopsy specimens is well established as the first line procedure for diagnosing colitis.<sup>49</sup> Ileoscopy with biopsy can be achieved with practice in at least 85% of colonoscopies and increases the diagnostic yield of CD in patients presenting with symptoms of IBD.<sup>49–52</sup> The most useful endoscopic features of CD are discontinuous involvement, anal lesions and cobble stoning. Colonoscopy assesses the anatomical severity of CD colitis with a high specificity. Anatomical criteria of severity are defined as deep ulcerations eroding the muscle layer, or mucosal detachments or ulcerations limited to the submucosa but extending to more than one third of a defined colonic segment (right, transverse, and left colon).<sup>53</sup> When there is severe, active disease, the value of full colonoscopy is limited by a higher risk of bowel perforation and diagnostic errors are more frequent. In these circumstances initial flexible sigmoidoscopy is safer and ileocolonoscopy postponed until the clinical condition improves.<sup>54</sup> The scoring of endoscopic disease activity in CD is reserved for clinical studies.<sup>10</sup> Ileoscopy is superior for the diagnosis of CD of the terminal ileum<sup>55–57</sup> when compared with radiology techniques, including MR and CT, specially for mild lesions. Capsule endoscopy and enteroscopy with biopsy by a push endoscope are safe and useful procedures for diagnosis of CD in selected patients with suggestive symptoms after failure of radiologic examinations.<sup>58</sup>

A plain abdominal radiograph is valuable in the initial assessment of patients with suspected severe CD by providing evidence of small bowel or colonic dilatation, calcified calculi, sacroiliitis, or the impression of a mass in the right iliac fossa. It is not a diagnostic test for CD.

## 2.3. Extent of disease

### 2.3.1. Procedures recommended for establishing the extent of CD

CD may affect the ileum out of reach of an endoscope, or involve more proximal small bowel (10% of patients.) Additionally, at the time of diagnosis 15.5% of patients have penetrating lesions (fistulas, phlegmons or abscesses).<sup>43</sup> Endoscopy and radiology are complementary techniques to define the site and extent of disease, so that optimal therapy can be planned.<sup>59–61</sup>

#### ECCO statement 2G

**MR and CT enterography or enteroclysis is an imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement and penetrating lesions in CD [EL1b, RGB]. Radiation exposure should be considered when selecting techniques. Because of the lower sensitivity of barium studies, alternative techniques are preferred if available. Transabdominal ultrasonography is a useful additional technique for assessing bowel inflammation.**

CT and MR are the current standards for assessing the small intestine. Both techniques can establish disease extension and activity based on wall thickness and increased intravenous contrast enhancement. The magnitude of these changes, along with presence of edema and ulcerations allow categorization of disease severity.<sup>61,62</sup> Both CT and MR are also the most accurate techniques to detect presence of extraluminal complications. Fluoroscopic examinations have a considerably lower sensitivity for the detection of small bowel and extraluminal lesions compared to CT or MR.<sup>64–66</sup>

CT and MR have a similar diagnostic accuracy for the detection of small intestine inflammatory lesions.<sup>55,67</sup> CT has greater availability and is less time-consuming than MR. The radiation burden from fluoroscopy and CT is appreciable.<sup>68</sup> Considering that these examinations need to be repeated over time and the young age of the IBD population, radiation exposure resulting from CT examination may entail an increased risk of cancer. Therefore, MR should be considered where possible.

CT and MR examinations of the small intestine require oral luminal contrast to achieve adequate distension.<sup>69</sup> Administration of luminal contrast by enteroclysis allows better small bowel distention than simple oral ingestion. However, nasojejunal tube placement entails radiation exposure and produces discomfort. The only study comparing both modalities in MR examinations concluded that bowel distension was inferior in MR follow-through, but diagnostic accuracy was similar using both methods.<sup>69</sup> Likewise, oral CT enterography has similar accuracy for enabling the detection of active Crohn's disease in comparison with CT enteroclysis with nasojejunal tube.<sup>62</sup> Oral ingestion of the luminal contrast provides adequate distension of the ileum. Enteroclysis may be necessary in selected cases in which upper CD lesions are suspected and adequate distention is not achieved with oral administration of the luminal contrast.

*Transabdominal ultrasound* (US) represents another non-ionizing imaging technique which may provide information

about disease activity, in particular for CD limited to the ileum.<sup>60</sup> Use of contrast-enhanced abdominal US<sup>70</sup> and Doppler US<sup>71,72</sup> may increase the sensitivity and specificity of this technique for the detection of disease activity. However, difficulty of visualization of deep bowel segments and high interobserver variability represent significant drawbacks. Nevertheless, in situations in which an overview of the inflammatory lesions is desirable, such as initial or emergency patient assessment, transabdominal US is a valuable, widely available, and inexpensive tool to judge site and extent of inflammation and possible complications.

*Leucocyte scintigraphy* is safe, non-invasive, and potentially permits assessment of the presence, extent, and activity of inflammation but radiation exposure and limited sensitivity, especially in patients under steroid treatment,<sup>73</sup> are leading to a reduced usage of this technique.

Evidence of the diagnostic yield of the above imaging techniques for assessment of colonic CD is growing, and seems to be highly dependent on technical details. MR has a high sensitivity and specificity for colonic inflammatory lesions when dark lumen (water enema) contrast and intravenous contrast are used, but diagnostic accuracy is considerably lower if these are not used.<sup>64,74,75</sup> The present data indicate that faecal tagging using barium instead of bowel cleansing is not suitable for MR colonography in CD.<sup>76</sup> Two studies evaluating the value of CT for the characterization of inflammatory lesions in the colon suggests a limited sensitivity of CT.<sup>77,78</sup> A single study also suggests a high sensitivity and specificity of water enema US for the evaluation of colonic CD.<sup>79</sup>

*Small bowel capsule endoscopy* (SBCE) has a higher sensitivity compared to MR or CT for the diagnosis of small bowel lesions, particularly for the detection of superficial mucosal lesions.<sup>57,80</sup> SBCE can be used as a first line test after exclusion of significant stenosis using a patency capsule or as second line in patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiology.

*Double balloon enteroscopy* (DBE) has also a higher sensitivity for the detection of small bowel lesions than radiological techniques.<sup>81</sup> However, completeness of small bowel assessment is limited by the severity of inflammatory lesions in proximal segments, and is associated to higher risks than SBCE. DBE should be used when tissue samples for pathological examinations are needed and when therapeutic maneuvers are required.

### 2.3.2. Procedures recommended for establishing the extent of stricturing CD

The procedures above (Section 2.3.1) apply to stricturing disease, but obstructive symptoms create their own challenge. The most reliable criterion for defining a stricture is a localised, persistent narrowing, whose functional effects may be judged from pre-stenotic dilatation.<sup>26</sup>

For the detection of stenosis in the colon and distal ileum ileocolonoscopy is recommended as the first choice, allowing tissue sampling for pathologic diagnosis. Complementary radiologic techniques to rule out additional stenotic lesions are necessary when the lesion is impassable with an endoscope.

Plain film radiography may identify small bowel obstruction but cannot depict the cause, making additional diagnostic workout based on MR or CT necessary. Both techniques are superior to conventional barium studies for detection of

stenotic lesions.<sup>63,81,82</sup> Direct comparison of CT and MR for the diagnosis of a variety of small intestine lesions including IBD, demonstrates a high sensitivity and specificity, similar in both techniques<sup>51</sup>. Comparison of enteroclysis and oral contrast administration on CT and MR examinations resulted in coincident results, showing a superior bowel distension when enteroclysis was used, but a similar diagnostic accuracy for the detection of stenotic lesions,<sup>62,69,83</sup> although enteroclysis may be superior for the demonstration of low grade stenosis.<sup>84</sup>

US is helpful in detecting pre-stenotic dilatation in small bowel strictures in severe cases that are candidates for surgery.<sup>85,86</sup> If colonoscopy is incomplete because of stricture, then MR or CT colonography (CT) can be used to evaluate colonic inflammatory lesions in the segments not explored by endoscopy. Differentiation between inflammatory and fibrostenotic strictures is crucial to the choice of therapy, but the diagnostic value of current techniques for making this distinction has not been adequately evaluated. CT and MRI can detect disease activity at a stricture based on the presence of edema, mucosal ulceration and contrast enhancement.<sup>85,87</sup> Contrast-enhanced Doppler US may also be valuable in determining disease activity within strictures.<sup>87–89</sup> However, the prognostic value of all these findings for response to medical treatment is still under investigation.

### 2.3.3. Procedures recommended for detecting extramural complications

#### ECCO statement 2H

**CT and MR are the recommended techniques for detection of extramural complications of CD [EL1b, RGA]. Transabdominal ultrasonography may also be used, but diagnostic accuracy is lower [EL2b, RGB].**

Both CT and MR are highly accurate for the detection of abscesses, fistulae and inflammatory conglomerates in CD.<sup>62,63,89,90</sup> Barium examinations have a considerably lower sensitivity compared to CT and MR for the detection of fistulas between the intestine and other organs, while for identification of enterocenteric fistulae barium studies have a similar sensitivity to CT and MR<sup>66</sup> The use of CT with positive oral contrast may be superior to MR for the distinction between an abscess and distended bowel loops within inflammatory conglomerates. Fistula formation around the affected or strictured bowel segment does provide a typical image when applying the MRE: the star-sign.<sup>91,92</sup>

US is an operator-dependent, but readily available, diagnostic tool for the diagnosis of extramural complications in CD. For the detection of fistulas and abscesses, respective sensitivities of 87% and 100% have been reported.<sup>93</sup> However diagnostic accuracy is higher for CT because of false positive results in US studies.<sup>94</sup>

### 2.3.4. Role of gastroduodenoscopy and biopsy in a patient with CD

CD involving the upper gastrointestinal tract is almost invariably accompanied by small or large bowel involvement.<sup>95–97</sup> Gastric biopsies may be useful when a patient has

colitis unclassified, as focal active gastritis in the absence of ulceration may be a feature of CD (Section 3.2.5).

### 2.3.5. Role of small bowel capsule endoscopy (SBCE) and double balloon enteroscopy (DBE) in suspected or proven CD

#### ECCO statement 2I

**Small bowel capsule endoscopy (SBCE) should be reserved for patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiological examinations (SBE/SBFT or CTE or MRE) [EL2; RG B].**

Double balloon enteroscopy (DBE) should be reserved for specific situations in which biopsy samples from suspected involved areas are important for diagnosis or in which a dilatation of strictures is reasonable [EL5, RG D].

SBCE is a novel method of directly visualising small bowel lesions in patients with IBD that may be missed by traditional endoscopic or radiological procedures. SBCE is a sensitive tool to detect mucosal abnormalities in the small bowel. The diagnostic yield (prevalence of abnormal findings) of SBCE is superior to other modalities (SBE/SBFT and CT enteroclysis) for diagnosing small bowel CD.<sup>65,80,98–104</sup> Contraindications for SBCE include gastrointestinal obstruction, strictures or fistulas, pacemakers or other implanted electromedical devices, and swallowing disorders.<sup>105</sup>

In cases of suspected CD, SBCE is likely to be more sensitive than other imaging modalities for diagnosis of mucosal lesions indicative of small bowel CD. A normal SBCE examination has a very high negative predictive value, essentially ruling out small bowel CD. However, the use of SBCE in cases of suspicion of small bowel CD is limited by a lack of specificity. CD associated lesions described by SBCE need more precise definition. Indeed, over 10% of healthy subjects demonstrate mucosal breaks and erosions in their SB. Thus, SBCE findings of mucosal lesions of the small bowel are not alone sufficient to establish a diagnosis of CD.

For some authors, SBCE could be used as a first line test. They recommend to use patency capsule either/or small bowel imaging before SBCE only if there is a suspicion of obstruction.<sup>106</sup> Because of the high frequency of partial obstruction, others recommend performing small bowel imaging (SBE/SBFT or CTE or MRE) systematically in patients with suspected CD.<sup>107</sup> Then, SBCE would be reserved for patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiological examinations. Large prospective studies are needed to position SBCE in a diagnostic algorithm for CD.

Among patients with proven CD, SBCE could be used to determine the extent and severity of lesions, post-operative recurrence and mucosal healing under therapies. In clinical practice, indications of SBCE are limited in patients with proven CD. It may be useful in the clinical setting of functional bowel disorders to assess whether inflammatory lesions are present.

The major advantages of double balloon enteroscopy (DBE) compared with SBCE are its ability to obtain biopsy samples and perform therapeutic measures during the procedure. There are specific situations in patients with CD in which a DBE may be useful.

In a recent study of a cohort of 40 patients with CD, DBE was found to be superior to small bowel follow-through imaging or barium enteroclysis for detecting erosions and small ulcerations in the distal ileum.<sup>108</sup> Biopsies can be taken when SBCE shows unclear small intestinal lesions. However, this should be restricted to patients in which definitive verification of jejunal or ileal involvement would have therapeutic implications.

The therapeutic potential of DBE has been demonstrated by reports of stricture dilatation and the retrieval of retained SBCE devices.

Risks include those inherent to endoscopy. In addition, risks associated with prolonged sedation time have to be considered. Further, it seems to be likely that CD patients undergoing DBE may have an increased risk of perforation due to possible adhesions, mucosal damage by the underlying diseases or adhesions after surgery.

### 2.3.6. Procedures recommended preoperatively

**ECCO statement 2J**  
Pre-operative imaging should follow strategies employed for the primary diagnosis of CD [EL5, RG D].

Small bowel mucosal lesions proximal to resection margins are found in about 65% of patients at the time of surgical intervention, most often undetected by radiography. These lesions do not, however, influence post-operative outcome if they are not obliterating the lumen.<sup>109,110</sup>

## 3. The histological diagnosis of Crohn's disease

During the last 25 years, several elements have influenced the accuracy of the histological diagnosis of Crohn's disease. The widespread introduction of colonoscopy allowed the analysis of multiple mucosal biopsies from different segments of the colon and the ileum. The introduction of new therapies inducing healing of the mucosa has made the pathologist aware of the impact of treatment upon the diagnostic features.

For this section articles reporting original research into the reproducibility, sensitivity or specificity of individual features for the histological diagnosis of Crohn's disease were sought from the literature using Medline and Pubmed. As further selection criteria, only those features which achieved moderate reproducibility judged by kappa value, or findings that were confirmed by subsequent studies, were considered. The purpose is to propose consensus guidelines for the histological diagnosis of Crohn's disease. The aspects discussed include: procedures required for a proper diagnosis; features which can be used for the analysis of endoscopic biopsies; features which can be used for the analysis of

surgical samples; and diagnostic criteria. Questions that are addressed include: how many features should be present for a firm diagnosis? Is it useful to search for dysplasia? What is the role of histology in management? Which features if any, can be used for assessment of disease activity?

### 3.1. Procedures for the diagnosis with endoscopic biopsies

#### 3.1.1. Number of biopsies

**ECCO statement 3A**  
For a reliable diagnosis of Crohn's disease "multiple" biopsies from five sites around the colon (including the rectum) and the ileum should be obtained. Multiple biopsies imply a minimum of two samples from each site [EL2, RG B].

**ECCO statement 3B**  
In patients with fulminant colitis, two samples from at least one site should be obtained [EL5, RG D].

For the initial diagnosis, analysis of a full colonoscopic biopsy series, rather than a single rectal biopsy, produces the most reliable diagnosis of Crohn's disease.<sup>111-119</sup> Samples are preferably obtained both from areas which are involved by the disease and from uninvolved areas. During follow up examinations, a smaller number of biopsy samples may be useful to confirm the diagnosis. In post-surgical follow up, biopsies of the neo-terminal ileum are indicated when disease recurrence is suspected. Where patients have undergone ileal pouch-anal anastomosis, biopsies of the afferent limb are indicated when Crohn's disease is suspected. Multiple biopsies are indicated when the patient was investigated during screening for dysplasia (=intraepithelial neoplasia).

#### 3.1.2. Handling of biopsies

**ECCO statement 3C**  
The biopsy samples should be accompanied by clinical information including the age of the patient, duration of disease and duration and type of treatment [EL5, RG D].

**ECCO statement 3D**  
All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport [EL5, RG D].

**ECCO statement 3E**

Since lesions may be mild or focal it is recommended that multiple sections from each sample are examined [EL2, RG B].

Biopsies from different regions should be handled in a way that the region of origin can be identified. This can be done by using different containers, multi-well cassettes or an acetate strip. Orientation of the samples using filter paper (submucosal side down) before fixation, may yield better results, because it allows a better assessment of architectural abnormalities [EL5, RG D]. The ideal number of sections to be examined in routine practice is not established, but numbers vary between 2 and 6 in different studies.<sup>118,119</sup> The diagnostic yield increases when more sections are examined. It is not clear whether serial-sections or step-sections from different levels of the sample should be examined. In one comparative study of rectal biopsies, serial-sectioning increased the ability to detect focal abnormalities including granulomas compared to step-sectioning. Confirmation of this finding is needed.<sup>120</sup> In routine practice, step-sections may be the simplest procedure. Obtaining two or three tissue levels has been proposed, each consisting of five or more sections.<sup>121</sup> Routine staining with haematoxylin and eosin are appropriate for diagnosis. [EL5, RG D]. At present special stains, immunohistochemistry, or other techniques for diagnostic purposes are not needed routinely.

This proposal is in agreement with guidelines proposed by the German, Austrian and Swiss Inflammatory Bowel Disease Study groups and the British Society of Gastroenterology initiative.<sup>116,122–126</sup> The use of multiple biopsies from different sites is supported by the expert opinion of clinicians, except for patients presenting with fulminant colitis. Fifty-eight percent of the clinicians agree to take 2 samples from one or two regions in fulminant colitis. Eight percent do not perform endoscopy in fulminant colitis and 34% would take only one sample. The proposal to use multiple biopsies for the diagnosis of Crohn's disease is supported by data from the literature.<sup>112,113</sup> For fulminant colitis, there are no appropriate data available.

## 3.2. Diagnostic features

### 3.2.1. Combined microscopic features

**ECCO statement 3F**

Focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation and patchy chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally accepted microscopic features which allow a diagnosis of Crohn's disease [EL2, RG B]. The same features and, in addition, an irregular villous architecture, can be used for analysis of endoscopic biopsy samples from the ileum. If the ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution [EL2, RG B].

A large variety of microscopic features have been identified which help to establish a diagnosis of Crohn's disease, and reported in the literature. They are summarized in Table 3.1. The reproducibility of these features, as well as sensitivity and specificity has been studied repeatedly (Section 3.2.5).

### 3.2.2. Focal or patchy inflammation

Focal or patchy chronic inflammation means a variable increase in lamina propria cellularity across the biopsy specimen and not confined to the superficial zone. A focal increase implies a normal background cellularity with a localised increase in cells. Patchy increase means an abnormal background cellularity with variable intensity. Focal or patchy increase should not be confused with the presence of normal lymphoid aggregates. Differences in cellularity between multiple biopsy specimens can be assessed with greater reproducibility than variation within a single specimen.

### 3.2.3. Crypt irregularity

Crypt irregularity implies crypt abnormalities in >10% of the crypts when focal or patchy inflammation is present. Crypt irregularity can be either crypt distortion (non-parallel crypts, variable diameter or cystically dilated crypts), crypt branching and crypt shortening.<sup>116</sup> The presence of more than two branched crypts in a well-orientated biopsy specimen can be regarded as abnormal.<sup>116</sup>

### 3.2.4. Granulomas

The granuloma in Crohn's disease is defined as a collection of epithelioid histiocytes (monocyte/macrophage cells), the outlines of which are often vaguely defined. Multinucleated giant cells are not characteristic and necrosis is usually not apparent. Only granulomas in the lamina propria not associated with active crypt injury may be regarded as a corroborating feature of Crohn's disease. Granulomas associated with crypt injury are less reliable features.<sup>127</sup> Non-caseating granulomas, small collections of epithelioid histiocytes and giant cells, or isolated giant cells can be observed in infectious colitis (granulomas suggest *Mycobacterium* sp., *Chlamydia* sp., *Yersinia pseudotuberculosis*, and *Treponema* sp.; microgranulomas suggest *Salmonella* sp., *Campylobacter* sp., and *Yersinia enterocolitica*; and giant cells suggest *Chlamydia* sp.) and must not be regarded as evidence for Crohn's disease. In patients living in or originating from areas with a high prevalence of tuberculosis, intestinal tuberculosis should be actively excluded in patients with suspected Crohn's disease. This is of particular relevance before starting anti TNF therapy.

### 3.2.5. Number of features needed for diagnosis

The selection of these features is based upon a systematic literature review. They achieve a diagnostic sensitivity and specificity of at least 50% and a moderate to good reproducibility (kappa of 0.4 or percentage agreement of at least 80%).<sup>119,120,128,129</sup> They were presented to a panel of experts and scored according to the quality of the study and expert opinion. Focal crypt irregularity scored highest on the evidence of more than one valid study of adequate size and from expert opinion; focal or patchy chronic inflammation was validated by evidence from single paper and expert

**Table 3.1** Microscopic features used for the diagnosis of Crohn's disease.

<i>Colon</i>	
Architecture	
Crypt architectural irregularity	Focal Diffuse
Reduced crypt numbers/mucosal atrophy	
Irregular surface	
Chronic inflammation	
Distribution I	Focal increase in intensity Patchy increase Diffuse increase
Distribution II	Superficial Transmucosal Basal plasma cells
Granulomas	
Mucin granulomas	
Polymorph inflammation	
Lamina propria	
Crypt epithelial polymorphs	
	Focal Diffuse
Crypt abscess	
Polymorph exudates	
Epithelial changes	
Erosion/ulceration	
Mucin	Depletion Preservation
Paneth cells distal to hepatic flexure	
Epithelial associated changes	
Increased intraepithelial lymphocytes >15	
<i>Terminal ileum</i>	
Architecture	
Villus irregularity	
Crypt architecture irregularity	
Epithelial changes	
Pseudopyloric gland metaplasia (ulcer associated cell lineage–UACL)	
<i>Comparison between different segments</i>	
Distribution of inflammation along the colon: gradient from proximal to distal	
Ratio of number of biopsies with focal cell infiltration to number of biopsies with mononuclear cell infiltration	

opinion. The features were also tested in a workshop, involving non-expert and expert pathologists and selected by 50% or more of the pathologists correctly identifying each case.<sup>112</sup> The patchy nature of the inflammation is only diagnostic in untreated adult patients. Inflammation can become patchy in ulcerative colitis under treatment, and young children (age <10 years) with ulcerative colitis may present with discontinuous inflammation.<sup>130–135</sup>

The presence of one single feature is not regarded as sufficient for a firm diagnosis. For single or multiple endo-

scopic samples there are no data available as to how many features must be present for a firm diagnosis of Crohn's disease. For surgical material, it has been suggested that a diagnosis of Crohn's disease should be made when three features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature provided that specific infections are excluded [EL5, RG D].<sup>125</sup> The same definition could be proposed for mucosal samples obtained during endoscopy. The following features can be identified in the mucosa and thus in endoscopic biopsy samples: granulomas and focal (segmental or discontinuous) crypt architectural abnormalities, in conjunction with focal or patchy chronic inflammation (chronic is defined as presence of lymphocytes and plasma cells), or mucin preservation at active sites. These are, therefore, potentially reliable markers for the diagnosis of Crohn's disease.

The majority of the expert clinicians (91%) and all pathologists agree that the presence of a granuloma and at least one other feature establishes a diagnosis of Crohn's disease. The second feature can be either inflammation (focal) or, preferably, architectural abnormalities. A pseudovillous appearance of the colorectal surface is more predictive of ulcerative colitis, while focal architectural abnormalities favour Crohn's disease. However, finding a granuloma is not always necessary for a diagnosis of Crohn's disease. Additional features which have been found to be useful are increased intraepithelial lymphocytes,<sup>112</sup> transmucosal inflammation,<sup>128</sup> focal chronic inflammation without crypt atrophy, focal cryptitis (although reproducibility is poor),<sup>116,136</sup> aphthoid ulcers, disproportionate submucosal inflammation, nerve fibre hyperplasia<sup>137</sup> and proximal location of ulceration and architectural distortion. When multiple biopsies are available, ileal involvement and a distribution of the inflammation showing a proximal to distal gradient can also be useful. The absence of features that are highly suggestive or diagnostic of ulcerative colitis, such as diffuse crypt irregularity; reduced crypt numbers and general crypt epithelial polymorphs, can also orient towards a diagnosis of Crohn's disease.

In difficult cases, gastric biopsies might help establish the diagnosis of Crohn's disease by the presence of granulomas or focally-enhanced or focal active gastritis. The latter is characterized by the absence of *Helicobacter pylori* and the presence of a perifoveolar or periglandular cellular infiltrate composed of mononuclear cells (CD3<sup>+</sup> T cells and CD68<sup>+</sup> cells) and granulocytes. Focal gastritis is not exclusive to Crohn's disease [EL4, RG C].<sup>138–142</sup>

### 3.3. Histology and dysplasia–intraepithelial neoplasia

#### ECCO statement 3G

The microscopic features for the diagnosis and grading of dysplasia–intraepithelial neoplasia of the colon in Crohn's disease are the same as those proposed for ulcerative colitis and, similarly, a second opinion is recommended for a firm diagnosis [EL2, RG B].

**ECCO statement 3H**

As for ulcerative colitis, sporadic adenomas may be difficult to distinguish from dysplasia-associated lesions or masses (DALM). The distinction is however important, because the management of sporadic adenomas differs from that of colitis-associated dysplasia. The patient's age, the site and morphology of the lesion, along with biopsies of flat surrounding mucosal, may be helpful in this distinction [EL2, RG B].

**3.3.1. Number of biopsies**

Patients with extensive Crohn's colitis carry an increased risk of colorectal cancer. Endoscopy with biopsy can be used for secondary prevention and the detection of dysplasia (intraepithelial neoplasia) in ulcerative colitis [EL2, RG C]. The optimal number of biopsies required for a reliable diagnosis of intraepithelial neoplasia has not been established. It has been proposed that 6 to 10 samples from different sites in the colon should be obtained, as suggested for ulcerative colitis. The current recommendation is to biopsy the colon at 10 cm intervals. Biopsies are labelled separately so that the segment of colon from which the tissue is obtained can be subsequently identified. It has been estimated that 33 biopsy specimens are required to give 90% confidence in the detection of dysplasia if it is indeed present.<sup>143</sup> These studies on ulcerative colitis have not been replicated in Crohn's colitis. The focal nature of inflammation in Crohn's colitis, the possibility of strictures and the prevalence of segmental resection means that surveillance practice in ulcerative colitis cannot be transferred directly to Crohn's colitis. The purpose of this section is not designed to make surveillance recommendations, but to acknowledge that if it is performed then the number of biopsies necessary to detect dysplasia is large. The use of targeted biopsies, aimed at lesions identified by chromoendoscopy or endomicroscopy, has changed the policy of taking biopsies in ulcerative colitis and this policy should also be considered in patients with Crohn's colitis.

**3.3.2. Microscopic features**

Microscopic features that are used for a diagnosis of intraepithelial neoplasia include architectural and cytological abnormalities. Architectural abnormalities are crowding of glands, thickening of the mucosa, and lengthening and distortion of the crypts with excessive budding and increased size. Surface and crypts are lined by tall, high columnar cells in which there is some mucus differentiation. Mucin tends to be in columnar cells rather than in the usual goblet cells. Nuclear changes are morphologically similar to those seen in tubular adenomas: hyperchromatic and enlarged nuclei, with nuclear crowding and frequent overlapping. The nuclei are also typically stratified. Mitotic figures may be present in the upper part of the crypt, and even in the surface (which is abnormal).<sup>144,145</sup>

**3.3.3. Additional techniques**

The use of additional techniques (including flow cytometry, immunohistochemistry) and the search for markers (such as the expression of p53) can be helpful for solving diagnostic problems and to support the diagnosis of intraepithelial neoplasia. These techniques, however, identify changes that are not entirely the same as dysplastic changes, which represent a complex phenomenon. Therefore, and because of practical availability and costs, the simple morphological recognition of dysplasia remains important for the management of the cancer risk in Crohn's disease.

**3.4. Surgery and pathology****ECCO statement 3I**

A surgical sample needs a complete gross examination, carried out in an orderly and systematic manner, including photographic documentation, preferably at the time when the specimen is removed [EL5, RG D]. Once gross observations are completed, the sample is opened along its longitudinal axis (along the antimesenteric or antimesocolic border, except perhaps at the sites of any carcinoma, where it may be preferable to leave that small segment unopened during fixation) and specimens for microscopy are collected, including the lymph nodes, terminal ileum and appendix [EL2, RG B].

**ECCO statement 3J**

The optimum number of samples from a colectomy specimen that should be obtained has not been established. However, multiple samples will improve the diagnostic yield. It is a mistake to sample only visible lesions. The samples can be processed routinely [EL5, RG D].

When surgical samples are available, the macroscopic aspects of the condition and the transmural character of the disease can be identified and in general many more features can be used for diagnostic purposes.<sup>137,146</sup> The features are summarized in Tables 3.2 and 3.3. Fat wrapping has a high predictive value for the diagnosis of Crohn's disease.<sup>115,116</sup>

**3.5. Histology and disease activity****ECCO statement 3K**

The pathology report should give an indication of the activity of the disease. Inactivity in the biopsy may not reflect inactivity in the patient [EL5, RG D].

Histology is routinely used for the diagnosis of ulcerative colitis (UC) and Crohn's disease (CD). The occurrence of healing of mucosal inflammation has already been noted as a feature of resolution in UC. Therefore, biopsies are used to discriminate between quiescent disease, inactive disease and different grades of activity in UC. This has led to the introduction of scoring systems for the assessment of disease activity in UC and their use in clinical drug trials.<sup>143</sup>

In contrast with UC, disease activity is not generally assessed by pathologists for CD. This is mainly due to the discontinuous character of the disease, inducing sampling error and the fact that the ileum may be the only area involved. Sampling error is very important, especially when only rectal biopsies are available. Microscopic analysis of multiple samples from different segments of the colon and ileum might provide useful information and allow an assessment of disease activity. Arguments in favour come from other diseases such as UC and *H. pylori*-related gastritis and from clinical drug trials. In UC, basal plasmacytosis can also help to predict relapse, while adequate control of inflammation seems important for the prevention of the development of cancer,<sup>147–152</sup> but neither have yet been studied in Crohn's disease. The data available on histology and activity for Crohn's disease are limited. Several clinical drug trials have shown that medical treatment can alter the mucosal histology, promoting healing and normalisation of the mucosa.<sup>151–158</sup> There is, however, no general agreement among expert clinicians about the use of microscopy to assess disease activity. If biopsies are used, then multiple samples have to be obtained and analysed. The presence of epithelial damage in association with neutrophils is a marker of disease activity.<sup>149</sup> In Crohn's disease a multivariate logistic regression model showed that severe lymphocytic (and eosinophilic) infiltration of the lamina propria, presence of crypt atrophy and absence of lymphocytic infiltration of the epithelium are the best variables for predicting uncomplicated disease.<sup>159</sup>

#### 4. Classification of Crohn's disease

Principal changes with respect to the 2004 ECCO guidelines.

- The use of the Montréal classification of clinical CD phenotypes is advocated [statement 4A].
- The course of CD may be predicted by clinical factors at diagnosis [statement 4B].

**Table 3.2** Macroscopic features for the diagnosis of Crohn's disease.

<ul style="list-style-type: none"> <li>-Ileal disease*</li> <li>-Rectum typically spared</li> <li>-Confluent deep linear ulcers, aphthoid ulcers</li> <li>-Deep fissures</li> <li>-Fistulae</li> <li>-Fat wrapping*</li> <li>-Skip lesions (segmental disease)</li> <li>-Cobblestoning</li> <li>-Thickening of the intestinal wall*</li> <li>-Strictures</li> </ul>
---

\* Typical discriminating features for a diagnosis of Crohn's disease as opposed to other conditions.

**Table 3.3** Microscopic features for the diagnosis of Crohn's disease in surgical specimens.

<ul style="list-style-type: none"> <li>-Transmural inflammation*</li> <li>-Aggregated inflammatory pattern, transmural lymphoid hyperplasia*</li> <li>-Submucosal thickening (expansion by fibrosis–fibromuscular obliteration and inflammation)</li> <li>-Fissures</li> <li>-Sarcoid granuloma (including in lymph nodes)*</li> <li>-Abnormalities of the enteric nervous system (submucosal nerve fibre hyperplasia and ganglionitis)*</li> <li>-Relatively unchanged epithelia–mucin preservation (goblet cells often normal)</li> </ul>
---

\* Typical discriminating features for a diagnosis of Crohn's disease as opposed to other conditions.

Disease classification is an important step to provide appropriate tools that enable us to dissect differences in the features and behaviour of Crohn's disease. Several ways of classifying CD have been used in the past. CD has been classified by disease phenotype (Rome or Vienna classification, modified in Montréal), by disease activity (mostly according to the Crohn's Disease Activity Index, CDAI), and by response to therapy (mainly steroids: 'steroid-resistant' or 'steroid-dependent', above). Since there is a strong trend toward the prescription of earlier and more aggressive maintenance therapies, some efforts are currently made to predict at diagnosis the subsequent phenotype of the disease, in order to adapt the level of the therapy to the severity of the disease. Some rough clinical predictors have been recently identified. In addition, there is an intense research devoted to the identification of genetic and serological predictors, so that it may hopefully be possible in the next few years to build an accurate, composite, and predictive index.

##### 4.1. General recommendations

###### ECCO statement 4A

The use of Montréal classification of Crohn's disease is advocated. No evidence-based recommendation can be made at this time to implement the routine clinical use of genetic tests or serological markers to classify Crohn's disease.

###### ECCO statement 4B

The course of Crohn's disease may be predicted by clinical factors at diagnosis (including young age, ileocolonic location and perianal disease) which should be taken into account when determining the initial therapeutic strategy [EL2b RG C].

**ECCO Statement 4C**

**Serum levels of CRP are useful for assessing a patient's risk of relapse [EL2b, RG B]. High CRP levels are indicative of active disease [EL2a, RG B] or a bacterial complication [EL3, RG C]. CRP levels can be used to guide therapy and follow up [EL2a, RG B].**

## 4.2. Specific components

### 4.2.1. Montréal phenotype classification

The Montréal revision (2005)<sup>160,161</sup> of the Vienna classification<sup>162</sup> is now regarded as the international standard of phenotype subtyping in Crohn's disease. Two major adjustments have been made in the Montréal classification. First, regarding disease location, the upper GI location (L4) is now added to the three major ones (terminal ileum (L1), colon (L2) and ileocolon (L3)) instead of being considered a mutually exclusive category. Second, regarding disease behaviour categories (non-stricturing non-penetrating (B1), structuring (B2) and penetrating (B3)), perianal fistulae and abscesses are no longer included in the penetrating phenotype that is now defined as "the occurrence of intra-abdominal fistulae, inflammatory masses and/or abscesses at any time in the course of the disease". The occurrence of perianal fistulae and abscesses is now indicated by a 'p' (for perianal) appended to B1, B2 or B3. It is established that in adult patients, location subtyping remains stable over time after diagnosis whereas the distribution of behaviour phenotype in patient populations changes continuously over time, with an increasing number of patients progressing from non-penetrating, non-structuring disease, to structuring or penetrating disease.<sup>163,164</sup> The superiority of Montréal classification over the Vienna classification in detecting early changes in Crohn's disease behaviour phenotype, associated with the need for subsequent major surgery, has been validated in a non-white population.<sup>165</sup>

### 4.2.2. Clinical predictors at diagnosis of subsequent phenotype

Increasing evidence suggests that early intensive therapy in Crohn's disease with immunomodulators and/or biologics is associated with an increased probability of mucosal healing and early sustained remission without steroids.<sup>166,167</sup> Given the risks of immunosuppressive therapy, only patients who would have experienced spontaneously a disabling and/or severe disease on a mid-term basis after diagnosis should be considered for early intensive therapy. There is no consensual definition of a disabling and/or severe disease but all or some of the following severity factors are usually used for defining a severe evolution within the first years of the disease: sustained disabling symptoms and impaired quality of life, repeated flare-ups with or without hospitalisation, development of irreversible penetrating and/or stricturing lesions, need for repeated courses of steroids and need for surgery. Using various combinations of these criteria, concordant data from three independent patient cohorts (two from referral centres<sup>168,169</sup> and one population-based<sup>170</sup>) suggest that the presence of perianal lesions and/or ileocolonic location and/

or young age at diagnosis together with the need for treating the first flare with steroids is associated with a high risk of disabling disease within the 5-year period after diagnosis. When two or more predictors are present in an individual patient, early treatment with thiopurines and/or biologics should be considered. (For an extensive review and guidelines on initiating immunosuppressive and biological therapy see Section 5.4 in Current Management).

### 4.2.3. Classification by serum CRP and faecal markers

It holds true that serum levels of CRP are useful for assessing a patient's risk of relapse [EL2b, RG B] and that high CRP levels are indicative of active disease [EL2a, RG B] or a bacterial complication [EL3, RG C]. A recent study suggests that high-sensitivity CRP could have a stronger association with disease activity<sup>171</sup> than that previously reported with standard CRP but these data must be reproduced before recommending the routine clinical use of high-sensitivity, instead of standard, CRP.

Growing evidence suggests that mucosal healing is a surrogate marker of sustained controlled Crohn's disease.<sup>167,172</sup> Endoscopy is still considered the standard for evaluation of mucosal healing but is invasive and costly. The faecal concentration of calprotectin and lactoferrin reflects the migration of neutrophils through the inflamed bowel wall to the mucosa. Both calprotectin and lactoferrin are stable, degradation-resistant proteins that can be easily measured in stools using enzyme-linked immunosorbent assay. Increased faecal levels of calprotectin and lactoferrin reflect intestinal inflammation of any cause, and in Crohn's disease they have a >90% positive predictive value for endoscopically active disease [EL2b, RGB].<sup>173</sup> As for serum CRP, the limit of the accuracy of faecal markers is that some patients have endoscopically active disease and faecal protein levels within the normal range, more often in the case of ileal than colonic disease.<sup>173,174</sup> However, the 60 to 70% sensitivity of raised faecal markers for predicting concurrent endoscopically active disease is superior to that of serum CRP and clearly superior to CDAI.<sup>173</sup> In summary, faecal levels of calprotectin or lactoferrin are emerging as a surrogate marker of mucosal healing, but the predictive value of uniform thresholds at an individual level has not been clearly demonstrated.

### 4.2.4. Correlation between genetic and serological markers and phenotype

Genome wide association defines more than 30 distinct susceptibility loci for Crohn's disease.<sup>175</sup> However, none of them is associated with an individual risk for developing the disease high enough to justify the routine use of genetic tests. Regarding genotype-phenotype correlations, only NOD2 variants and 5q31 susceptibility haplotype have been reproducibly shown to be associated with ileal location and penetrating perianal disease, respectively.<sup>176,177</sup> In contrast, recent concordant data suggest a significant relationship between the severity of Crohn's disease and the presence and levels of serological markers. Using slightly different panels of serological markers, the number and magnitude of immune responses to different microbial antigens were shown to be associated with the severity of the disease, characterized by the occurrence of stricturing/penetrating lesions and the need for surgery.<sup>176</sup> However, at diagnosis,

the positive predictive value of serological markers for subsequent disease course appears to be limited.<sup>176</sup>

#### 4.2.5. Need for a composite predictive index at diagnosis

Given the complex benefit–risk balance of early aggressive therapeutic strategies using immunomodulators and biologics in CD, there is an increasing need for identifying at diagnosis patients who are likely to develop severe or complicated disease. Simple clinical predictors have been identified, but their individual accuracy remains limited. Genetic factors and serological markers of immune reactivity, considered alone or in combination, have been so far unhelpful in predicting the future course of CD at diagnosis. This is why further studies are needed to assess collectively all potential predictors in large, phenotypically well-defined cohorts, in order to build an accurate composite predictor index.

### Contributors

**M. Allez**, Hopital Saint-Louis, Paris, France  
**L. Beaugerie**, Hôpital Saint-Antoine, Paris, France  
**A. Dignass**, Markus Krankenhaus, Frankfurter Diakonie-Kliniken, Frankfurt/Mainz, Germany  
**J. Karagiannis**, Agia Olga Hospital, Athens, Greece  
**E. Louis**, CHU Liège, Liege, France  
**L. Kupcinkas**, Kaunas, Lithuania  
**G. Mantzaris**, Evangelismos Hospital, Athens, Greece  
**Th. Ochschenkühn**, IBD Center of the University of Munich, Munich, Germany  
**T. Orchard**, St Mary's Hospital, Imperial Collge Healthcare NHS Trust, London, United Kingdom  
**J. Panes**, Hospital Clinic Barcelona, Barcelona Spain  
**G. Rogler**, Universitätsspital Zürich, Zürich, Switzerland  
**E. Stange**, Robert Bosch Krankenhaus, Stuttgart, Germany  
**S. Travis**, John Radcliffe Hospital, Oxford, United Kingdom  
**G. van Assche**, University Hospital Gasthuisberg, Leuven, Belgium

### Acknowledgements

We wish to acknowledge the secretarial assistance of N. Eichinger, ECCO secretariat, Vienna, Austria.

The Contributors to the consensus meeting were:

**Austria:** Novacek, Reinisch, Tilg  
**Belgium:** De Vos, D'Haens, D'Hoore, Louis, Vermeire, van Assche  
**Croatia:** Vucelic  
**Czech Republic:** Lukas  
**Finland:** Kolho  
**France:** Allez, Beaugerie, Bouhnik, Carbonnel, Colombel, Lemann, Marteau  
**Germany:** Baumgart, Dignass, Herrlinger, Jehle, Kiesslich, Koletzko, Ochschenkühn, Reinshagen, Stange, Sturm  
**Ireland:** O'Morain  
**Israel:** Dotan  
**Italy:** Ardizzone, Danese, Gionchetti, Guslandi  
**Lithuania:** Kupcinkas  
**Netherlands:** Hommes, Oldenburg, van der Woude, Escher  
**Portugal:** Portela

**Spain:** Gassull, Gomollon, Panes, Rimola

**Norway:** Öresland

**Sweden:** Söderholm

**Switzerland:** Michetti, Mottet, Rogler

**United Kingdom:** Cole, Lindsay, Orchard, Windsor, Travis

### References

- Shivananda S, Lennard-Jones J, Logan R, Fear N, Price A, Carpenter L, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between the north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996;**39**:690–7.
- Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;**53**(Suppl 5):V1–V16.
- Stange EF, Schreiber S, Fölsch UR, von Herbay A, Schölmerich J, Hoffmann J, et al. Diagnostik und Therapie des M. Crohn-Ergebnisse einer evidenzbasierten Konsensuskonferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten. *Z Gastroenterol* 2003;**41**:19–68.
- Travis SP, Stange EF, Lémann M, Oresland T, Chowers Y, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* Mar 2006(Suppl 1):i16–35.
- Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006;**55**(Suppl 1):i1–i15.
- Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health* 1984;**74**:979–83.
- Anonymous, Centre for Evidence Based Medicine, Oxford. Levels of evidence and grades of recommendation. [http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp).
- Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology* 2004;**126**:1257–69.
- Irvine EJ. Assessing outcomes in clinical trials. In: Satsangi J, Sutherland LR, editors. Inflammatory bowel diseases. London: Churchill Livingstone; 2003. p. 319–33.
- Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002;**122**:512–30.
- 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**:1490–4.
- Brignola C, Iannone P, Pasquali S, Campieri M, Gionchetti P, Belluzzi A, et al. Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. *Dig Dis Sci* 1992;**37**:29–32.
- Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**:761–9.
- Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
- Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.

16. Caprilli R, Andreoli A, Capurso L, Corrao G, D'Albasio G, Gioieni A, et al & Gruppo Italiano per lo Studio del Colon e del Retto (GISC). Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of CD. *Aliment Pharmacol Ther* 1994;**8**:35–43.
17. Simrén M, Axelsson J, Gillberg, Abrahamsson H, Svedlund J, Björnsson ES. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;**97**:389–96.
18. Loftus Jr EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**(6):1504–17.
19. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004;**126**(6):1518–32.
20. American Gastroenterological Association medical position statement: guidelines for the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;**116**(6):1461–3.
21. Burgmann T, Clara I, Graff L, Walker J, Lix L, Rawsthorne P, et al. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis—how much is irritable bowel syndrome? *Clin Gastroenterol Hepatol* 2006;**4**(5): 614–20.
22. Pimentel M, Chang M, Chow EJ, Tabibzadeh S, Kirit-Kiriak V, Targan SR, et al. Identification of a prodromal period in Crohn's disease but not ulcerative colitis. *Am J Gastroenterol* 2000;**95** (12):3458–62.
23. Lennard-Jones JE, Shivananda S. Clinical uniformity of inflammatory bowel disease a presentation and during the first year of disease in the north and south of Europe. EC-IBD Study Group. *Eur J Gastroenterol Hepatol* 1997;**9**(4):353–9.
24. Farmer RG, Hawk WA, Turnbull Jr RB. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology* 1975;**68**(4 Pt 1):627–35.
25. Schwartz DA, Loftus Jr EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002;**122**(4):875–80.
26. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A): 5–36.
27. Price AB. Overlap in the spectrum of non-specific inflammatory bowel disease—'colitis indeterminate'. *J Clin Pathol* 1978;**31** (6):567–77.
28. Andersson RE, Olaison G, Tysk C, Ekbohm A. Appendectomy is followed by increased risk of Crohn's disease. *Gastroenterology* 2003;**124**(1):40–6.
29. Bridger S, Lee JC, Bjarnason I, Jones JE, Macpherson AJ. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis. *Gut* 2002;**51**(1):21–5.
30. Garcia Rodriguez LA, Ruigomez A, Panes J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* 2006;**130**(6):1588–94.
31. Reinisch W, Miehsler W, Dejaco C, Harrer M, Waldhoer T, Lichtenberger C, et al. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther* 2003;**17**(11):1371–80.
32. Fagan EA, Dyck RF, Maton PN, Hodgson HJ, Chadwick VS, Petrie A, et al. Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur J Clin Invest* 1982;**12**(4):351–9.
33. Poullis AP, Zar S, Sundaram KK, Moodie SJ, Risley P, Theodossi A, et al. A new, highly sensitive assay for C-reactive protein can aid the differentiation of inflammatory bowel disorders from constipation- and diarrhoea-predominant functional bowel disorders. *Eur J Gastroenterol Hepatol* 2002;**14**(4):409–12.
34. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. *Inflamm Bowel Dis* 2004;**10**(5):661–5.
35. Sachar DB, Luppescu NE, Bodian C, Shlien RD, Fabry TL, Gumaste VV. Erythrocyte sedimentation as a measure of Crohn's disease activity: opposite trends in ileitis versus colitis. *J Clin Gastroenterol* 1990;**12**(6):643–6.
36. D'Inca R, Dal PE, Di LV, et al. Calprotectin and lactoferrin in the assessment of intestinal inflammation and organic disease. *Int J Colorectal Dis* 2007;**22**(4):429–37.
37. Gaya DR, Lyon TD, Duncan A, Neilly JB, Han S, Howell J, et al. Faecal calprotectin in the assessment of Crohn's disease activity. *QJM* 2005;**98**(6):435–41.
38. Tibble J, Teahon K, Thjodleifsson B, Roseth A, Sigthorsson G, Bridger S, et al. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000;**47**(4):506–13.
39. 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**(1):15–22.
40. Kane SV, Sandborn WJ, Rufo PA, Zholudev A, Boone J, Lyerly D, et al. Faecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. *Am J Gastroenterol* 2003;**98**(6):1309–14.
41. de Jong NS, Leach ST, Day AS. Faecal S100A12: a novel noninvasive marker in children with Crohn's disease. *Inflamm Bowel Dis* 2006;**12**(7):566–72.
42. Kaiser T, Langhorst J, Wittkowski H, Becker K, Friedrich AW, Rueffer A, et al. Faecal S100A12 as a non-invasive marker distinguishing inflammatory bowel disease from irritable bowel syndrome. *Gut* 2007;**56**(12):1706–13.
43. Mylonaki M, Langmead L, Pantes A, Johnson F, Rampton DS. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. *Eur J Gastroenterol Hepatol* 2004;**16**(8):775–8.
44. Bossuyt X. Serologic markers in inflammatory bowel disease. *Clin Chem* 2006;**52**(2):171–81.
45. Reese GE, Constantinides VA, Simillis C, Darzi AW, Orchard TR, Fazio VW, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006;**101**(10):2410–22.
46. Dubinsky MC, Kugathasan S, Mei L, Picorjnell Y, Nebel J, Wrobel I, et al. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008;**6**(10):1105–11.
47. Ferrante M, Henckaerts L, Joossens M, Pierik M, Joossens S, Dotan N, et al. New serological markers in inflammatory bowel disease are associated with complicated disease behaviour. *Gut* 2007;**56**(10):1394–403.
48. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2006;**55**(3): 426–31.
49. Coremans G, Rutgeerts P, Geboes K, Van den Oord J, Ponette E, Vantrappen G. The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn's disease. *Gastrointest Endosc* 1984;**30**(3):167–72.
50. Geboes K, Ectors N, D'Haens G, Rutgeerts P. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? *Am J Gastroenterol* 1998;**93**(2): 201–6.
51. Cherian S, Singh P. Is routine ileoscopy useful? An observational study of procedure times, diagnostic yield, and learning curve. *Am J Gastroenterol* 2004;**99**(12):2324–9.
52. 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**(4):947–53.
53. Nahon S, Bouhnik Y, Lavergne-Slove A, Bitoun A, Panis Y, Valleur P, et al. Colonoscopy accurately predicts the anatomical severity of colonic Crohn's disease attacks: correlation with findings from colectomy specimens. *Am J Gastroenterol* 2002;**97**(12):3102–7.
  54. Carter MJ, Lobo AJ, Travis SP. IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;**53**(Suppl 5):V1–V16.
  55. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008;**247**(1):64–79.
  56. Horsthuis K, Stokkers PC, Stoker J. Detection of inflammatory bowel disease: diagnostic performance of cross-sectional imaging modalities. *Abdom Imaging* 2008;**33**(4):407–16.
  57. Marshall JK, Cawdron R, Zealley I, Riddell RH, Somers S, Irvine EJ. Prospective comparison of small bowel meal with pneumocolon versus ileo-colonoscopy for the diagnosis of ileal Crohn's disease. *Am J Gastroenterol* 2004;**99**(7):1321–9.
  58. Tillack C, Seiderer J, Brand S, Göke B, Reiser MF, Schaefer C, et al. Correlation of magnetic resonance enteroclysis (MRE) and wireless capsule endoscopy (CE) in the diagnosis of small bowel lesions in Crohn's disease. *Inflamm Bowel Dis* 2008;**14**(9):1219–28.
  59. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasar El Yagi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;**49**(6):777–82.
  60. Fraquelli M, Colli A, Casazza G, Paggi S, Colucci A, Massironi S, et al. Role of US in detection of Crohn disease: meta-analysis. *Radiology* 2005;**236**(1):95–101.
  61. Koh DM, Miao Y, Chinn RJ, Amin Z, Zeegen R, Westaby D, et al. MR imaging evaluation of the activity of Crohn's disease. *AJR Am J Roentgenol* 2001;**177**(6):1325–32.
  62. Wold PB, Fletcher JG, Johnson CD, Sandborn WJ. Assessment of small bowel Crohn disease: noninvasive peroral CT enterography compared with other imaging methods and endoscopy—feasibility study. *Radiology* 2003;**229**(1):275–81.
  63. Gourtsoyiannis NC, Grammatikakis J, Papamastorakis G, Koutroumabakis J, Prassopoulos P, Rousomoustakaki M, et al. Imaging of small intestinal Crohn's disease: comparison between MR enteroclysis and conventional enteroclysis. *Eur Radiol* 2006;**16**(9):1915–25.
  64. Rimola J, Rodriguez S, Garcia-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in Crohn disease. *Gut* 2009.
  65. Albert JG, Martiny F, Krummenel A, Stock K, Lesske J, Göbel CM, et al. Diagnosis of small bowel Crohn's disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. *Gut* 2005;**54**(12):1721–7.
  66. Sailer J, Peloschek P, Schober E, Schima W, Reinisch W, Vogelsang H, et al. Diagnostic value of CT enteroclysis compared with conventional enteroclysis in patients with Crohn's disease. *AJR Am J Roentgenol* 2005;**185**(6):1575–81.
  67. Schmidt S, Lepori D, Meuwly JY, Duvoisin B, Meuli R, Michetti P, et al. Prospective comparison of MR enteroclysis with multi-detector spiral-CT enteroclysis: interobserver agreement and sensitivity by means of "sign-by-sign" correlation. *Eur Radiol* 2003;**13**(6):1303–11.
  68. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007;**357**(22):2277–84.
  69. Negaard A, Paulsen V, Sandvik L, Berstad AE, Borthne A, Try K, et al. A prospective randomized comparison between two MRI studies of the small bowel in Crohn's disease, the oral contrast method and MR enteroclysis. *Eur Radiol* 2007;**17**(9):2294–301.
  70. Biancone L, Calabrese E, Petruzzello C, Onali S, Caruso A, Palmieri G, et al. Wireless capsule endoscopy and small intestine contrast ultrasonography in recurrence of Crohn's disease. *Inflamm Bowel Dis* 2007;**13**(10):1256–65.
  71. Martinez MJ, Ripollés T, Paredes JM, Blanc E, Marti-Bonmati L. Assessment of the extension and the inflammatory activity in Crohn's disease: comparison of ultrasound and MRI. *Abdom Imaging* 2009;**34**(2):141–8.
  72. Rapaccini GL, Pompili M, Orefice R, Covino M, Riccardi L, Cedrone A, et al. Contrast-enhanced power doppler of the intestinal wall in the evaluation of patients with Crohn disease. *Scand J Gastroenterol* 2004;**39**(2):188–94.
  73. Sans M, Fuster D, Llach J, Lomena F, Bordas JM, Herranz R, et al. Optimization of technetium-99m-HMPAO leukocyte scintigraphy in evaluation of active inflammatory bowel disease. *Dig Dis Sci* 2000;**45**(9):1828–35.
  74. Ajaj WM, Lauenstein TC, Pelster G, Gerken G, Ruehm SG, Debatin JF, et al. Magnetic resonance colonography for the detection of inflammatory diseases of the large bowel: quantifying the inflammatory activity. *Gut* 2005;**54**(2):257–63.
  75. Dinter DJ, Chakraborty A, Brade J, Back W, Neff KW, Singer MV, et al. Endoscopy and magnetic resonance imaging in patients with Crohn's disease: a retrospective single-centre comparative study. *Scand J Gastroenterol* 2008;**43**(2):207–16.
  76. Langhorst J, Kuhle CA, Ajaj W, Nüfer M, Barkhausen J, Michalsen A, et al. MR colonography without bowel purgation for the assessment of inflammatory bowel diseases: diagnostic accuracy and patient acceptance. *Inflamm Bowel Dis* 2007;**13**(8):1001–8.
  77. Ota Y, Matsui T, Ono H, Uno H, Mataka H, Tsuda S, et al. Value of virtual computed tomographic colonography for Crohn's colitis: comparison with endoscopy and barium enema. *Abdom Imaging* 2003;**28**(6):778–83.
  78. Tarjan Z, Zagoni T, Györke T, Mester A, Karlinger K, Mako EK. Spiral CT colonography in inflammatory bowel disease. *Eur J Radiol* 2000;**35**(3):193–8.
  79. Bru C, Sans M, Defelitto MM, Gilabert R, Fuster D, Llach J, et al. Hydrocolonic sonography for evaluating inflammatory bowel disease. *AJR Am J Roentgenol* 2001;**177**(1):99–105.
  80. Voderholzer WA, Beinholdt J, Rogalla P, Murrer S, Schachschal G, Lochs H, et al. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005;**54**(3):369–73.
  81. Seiderer J, Herrmann K, Diepolder H, Schoenberg SO, Wagner AC, Göke B, et al. Double-balloon enteroscopy versus magnetic resonance enteroclysis in diagnosing suspected small-bowel Crohn's disease: results of a pilot study. *Scand J Gastroenterol* 2007;**42**(11):1376–85.
  82. Hara AK, Leighton JA, Heigh RI, Sharma VK, Silva AC, De Petris G, et al. Crohn disease of the small bowel: preliminary comparison among CT enterography, capsule endoscopy, small-bowel follow-through, and ileoscopy. *Radiology* 2006;**238**(1):128–34.
  83. Schreyer AG, Geissler A, Albrich H, Schölmerich J, Feuerbach S, Rogler G, et al. Abdominal MRI after enteroclysis or with oral contrast in patients with suspected or proven Crohn's disease. *Clin Gastroenterol Hepatol* 2004;**2**(6):491–7.
  84. Maccioni F, Bruni A, Viscido A, Colaiacono MC, Cocco A, Montesani C, et al. MR imaging in patients with Crohn disease: value of T2- versus T1-weighted gadolinium-enhanced MR sequences with use of an oral superparamagnetic contrast agent. *Radiology* 2006;**238**(2):517–30.
  85. Parente F, Maconi G, Bollani S, Anderloni A, Sampietro G, Cristaldi M, et al. Bowel ultrasound in assessment of Crohn's disease and detection of related small bowel strictures: a prospective comparative study versus x ray and intraoperative findings. *Gut* 2002;**50**(4):490–5.

86. Chiorean MV, Sandrasegaran K, Saxena R, Maglinte DD, Nakeeb A, Johnson CS. Correlation of CT enteroclysis with surgical pathology in Crohn's disease. *Am J Gastroenterol* 2007;102(11):2541–50.
87. Esteban JM, Aleixandre A, Hurtado MJ, Maldonado L, Mora FJ, Nogués E. Contrast-enhanced power Doppler ultrasound in the diagnosis and follow-up of inflammatory abdominal masses in Crohn's disease. *Eur J Gastroenterol Hepatol* 2003;15(3):253–9.
88. Kratzer W, von Tirpitz C, Mason R, Reinshagen M, Adler G, Möller P, et al. Contrast-enhanced power Doppler sonography of the intestinal wall in the differentiation of hypervascularized and hypovascularized intestinal obstructions in patients with Crohn's disease. *J Ultrasound Med* 2002;21(2):149–57.
89. Spalinger J, Patriquin H, Miron MC, Marx G, Herzog D, Dubois J, et al. Doppler US in patients with Crohn disease: vessel density in the diseased bowel reflects disease activity. *Radiology* 2000;217(3):787–91.
90. Masselli G, Casciani E, Poletti E, Lanciotti S, Bertini L, Gualdi G. Assessment of Crohn's disease in the small bowel: Prospective comparison of magnetic resonance enteroclysis with conventional enteroclysis. *Eur Radiol* 2006;16(12):2817–27.
91. Herrmann KA, Michaely HJ, Seiderer J, Ochsenukuehn T, Reiser MF, Schoenberg SO. The "star-sign" in magnetic resonance enteroclysis: a characteristic finding of internal fistulae in Crohn's disease. *Scand J Gastroenterol* 2006;41(2):239–41.
92. Herrmann KA, Michaely HJ, Zech CJ, Seiderer J, Reiser MF, Schoenberg SO. Internal fistulas in Crohn disease: magnetic resonance enteroclysis. *Abdom Imaging* 2006;31(6):675–87.
93. Gasche C, Moser G, Turetschek K, Schober E, Moeschi P, Oberhuber G. Transabdominal bowel sonography for the detection of intestinal complications in Crohn's disease. *Gut* 1999;44(1):112–7.
94. Maconi G, Sampietro GM, Parente F, Pompili G, Russo A, Cristaldi M, et al. Contrast radiology, computed tomography and ultrasonography in detecting internal fistulas and intra-abdominal abscesses in Crohn's disease: a prospective comparative study. *Am J Gastroenterol* 2003;98(7):1545–55.
95. Rutgeerts P, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: A clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980;12(6):288–94.
96. Wagtmans MJ, van Hogezaand RA, Griffioen G, Verspaget HW, Lamers CB. Crohn's disease of the upper gastrointestinal tract. *Neth J Med* 1997;50(2):S2–S7.
97. Witte AM, Veenendaal RA, van Hogezaand RA, Verspaget HW, Lamers CB. Crohn's disease of the upper gastrointestinal tract: the value of endoscopic examination. *Scand J Gastroenterol Suppl* 1998;100-5:100–5.
98. Chong AK, Taylor A, Miller A, Hennessy O, Connell W, Desmond P. Capsule endoscopy vs. push enteroscopy and enteroclysis in suspected small-bowel Crohn's disease. *Gastrointest Endosc* 2005;61(2):255–61.
99. Costamagna G, Shah SK, Riccioni ME, Foschia F, Mutignani M, Perri V, et al. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. *Gastroenterology* 2002;123(4):999–1005.
100. Eliakim R, Suissa A, Yassin K, Katz D, Fischer D. Wireless capsule video endoscopy compared to barium follow-through and computerised tomography in patients with suspected Crohn's disease—final report. *Dig Liver Dis* 2004;36(8):519–22.
101. Fireman Z, Mahajna E, Broide E, Shapiro M, Fich L, Sternberg A, et al. Diagnosing small bowel Crohn's disease with wireless capsule endoscopy. *Gut* 2003;52(3):390–2.
102. Golder SK, Schreyer AG, Endlicher E, Feuerbach S, Schölmerich J, Kullmann F, et al. Comparison of capsule endoscopy and magnetic resonance (MR) enteroclysis in suspected small bowel disease. *Int J Colorectal Dis* 2006;21(2):97–104.
103. Mow WS, Lo SK, Targan SR, Dubinsky MC, Treyzon L, Abreu-Martin MT, et al. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004;2(1):31–40.
104. Triester SL, Leighton JA, Leontiadis GI, Gurudu SR, Fleischer DE, Hara AK, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol* 2006;101(5):954–64.
105. Hommes DW, van Deventer SJ. Endoscopy in inflammatory bowel diseases. *Gastroenterology* 2004;126(6):1561–73.
106. Leighton JA, Legnani P, Seidman EG. Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. *Inflamm Bowel Dis* 2007;13(3):331–7.
107. Bruining DH, Loftus Jr EV. Crohn's disease clinical issues and treatment: what the radiologist needs to know and what the gastroenterologist wants to know. *Abdom Imaging* 2008.
108. Oshitani N, Yukawa T, Yamagami H, Inagawa M, Kamata N, Watanabe K, et al. Evaluation of deep small bowel involvement by double-balloon enteroscopy in Crohn's disease. *Am J Gastroenterol* 2006;101(7):1484–9.
109. Lescut D, Vanco D, Bonniere P, et al. Perioperative endoscopy of the whole small bowel in Crohn's disease. *Gut* 1993;34(5):647–9.
110. Whelan G, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. *Gastroenterology* 1985;88(6):1826–33.
111. Bentley E, Jenkins D, Campbell F, Warren B. How could pathologists improve the initial diagnosis of colitis? Evidence from an international workshop. *J Clin Pathol* 2002;55:955–60.
112. Dejaco C, Osterreicher C, Angelberger S, Püspök A, Birner P, Poetzi R, et al. Diagnosing colitis: a prospective study on essential parameters for reaching a diagnosis. *Endoscopy* 2003;35:1004–8.
113. Tanaka M, Riddell RH, Saito H, Soma Y, Hidaka H, Kudo H, et al. Morphologic criteria applicable to biopsy specimens for effective distinction of inflammatory bowel disease from other forms of colitis and of Crohn's disease from ulcerative colitis. *Scand J Gastroenterol* 1999;34:55–67.
114. Geboes K, Ectors N, D'Haens G, Rutgeerts P, et al. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of IBD. *Am J Gastroenterol* 1998;93:201–6.
115. Jenkins D, Balsitis M, Gallivan S, Dixon MF, Gilmour HM, Shepherd NA, et al. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* 1997;50:93–105.
116. Schumacher G, Kollberg B, Sandstedt B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis. Histologic course during the 1st year after presentation. *Scand J Gastroenterol* 1994;29:318–32.
117. Seldenrijk CA, Morson BC, Meuwissen SGM, Schipper NW, Lindeman J, Meijer CJ, et al. Histopathological evaluation of colonic mucosal biopsy specimens in chronic inflammatory bowel disease: diagnostic implications. *Gut* 1991;32:1514–20.
118. Theodossi A, Spiegelhalter DJ, Jass J, Firth J, Dixon M, Leader M, et al. Observer variation and discriminatory value of biopsy features in inflammatory bowel disease. *Gut* 1994;35:961–8.
119. Surawicz CM. Serial sectioning of a portion of a rectal biopsy detects more focal abnormalities. A prospective study of patients with inflammatory bowel disease. *Dig Dis Sci* 1982;27:434–6.
120. Goldman H. Colonic mucosal biopsy in inflammatory bowel disease. *Surgical Pathology* 1991;4:3–23.
121. Von Herbay A. Evidenz-basierte Leitlinien der DGVS für Diagnostik und Therapie beim Morbus Crohn. *Germany Z Gastroenterol* 2003;41:24–6.

122. Petritsch W, Feichtenschlager T, Gasche C, Hinterleitner T, Judmaier G, Knoflach P, et al. Diagnosis in chronic inflammatory bowel diseases – report of the Austrian Chronic Inflammatory Bowel Disease Study Group. *Acta Med Austriaca* 1998;**25**:37–43.
123. Hahne M, Riemann JF. Inflammatory bowel diseases: diagnosis (including new procedures for small intestine examination). *Schweiz Rundsch Med Prax* 2002;**91**:2023–8.
124. Lennard-Jones JE. Crohn's disease: definition, pathogenesis, aetiology. *Clin Gastroenterol* 1980(suppl 1):173–89 I.
125. Tanaka M, Saito H, Fukuda S, Sasaki Y, Munakata A, Kudo H, et al. Simple mucosal biopsy criteria differentiating among Crohn's disease, ulcerative colitis, and other forms of colitis. Measurement of validity. *Scand J Gastroenterol* 2000;**35**:281–6.
126. Mahadeva U, Martin JP, Patel NK, Price AB. Granulomatous ulcerative colitis: a re-appraisal of the mucosal granuloma in the distinction of Crohn's disease from ulcerative colitis. *Histopathology* 2002;**41**:50–5.
127. Bernades P, Hecketsweiler P, Benozio M, Descos L, Geffroy Y, Hemet J, et al. Proposition d'un système de critères pour le diagnostic des entérocolites inflammatoires cryptogénétiques (maladie de Crohn et Rectocolite Hémorragique). *Gastroentérologie Clin Biol* 1978;**2**:1047–54.
128. Jenkins D, Goodall A, Drew K. What is colitis? Statistical approach to distinguishing clinically important inflammatory change in rectal biopsy specimens. *J Clin Pathol* 1988;**41**:72–9.
129. Kleer CG, Appelman HD. Ulcerative colitis: patterns of involvement in colorectal biopsies and changes with time. *Am J Surg Pathol* 1998;**22**:983–9.
130. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. *Gastrointest Endosc* 1995;**42**:232–7.
131. Geboes K. Pathology of inflammatory bowel diseases (IBD): variability with time and treatment. *Colorectal disease* 2001;**3**:2–12.
132. Markowitz J, Kahn E, Grancher K, Hyams J, Treem W, Daum F. Atypical rectosigmoid histology in children with newly diagnosed ulcerative colitis. *Am J Gastroenterol* 1993;**88**:2034–7.
133. Robert ME, Tang L, Hao LM, Reyes-Mugica M. Patterns of inflammation in mucosal biopsies of ulcerative colitis. Perceived differences in pediatric populations are limited to children younger than 10 years. *Am J Surg Pathol* 2004;**28**:183–9.
134. Glickman JN, Bousvaros A, Farraye FA, Zholudev A, Friedman S, Wang HH, et al. Pediatric patients with untreated ulcerative colitis may present initially with unusual morphologic findings. *Am J Surg Pathol* 2004;**28**:190–7.
135. Tanaka M, Riddell RH. The pathological diagnosis and differential diagnosis of Crohn's disease. *Hepatogastroenterol* 1990;**37**:18–31.
136. Cook MG, Dixon MF. An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis. *Gut* 1973;**14**:255–62.
137. Ectors NL, Dixon MF, Geboes KJ, Rutgeerts PJ, Desmet VJ, Vantrappen GR. Granulomatous gastritis: a morphological and diagnostic approach. *Histopathology* 1993;**23**:55–61.
138. Shapiro JL, Goldblum JR, Petras RE. A clinicopathologic study of 42 patients with granulomatous gastritis. Is there really an idiopathic granulomatous gastritis. *Am J Surg Pathol* 1996;**20**:462–70.
139. Oberhuber G, Puspok A, Oesterreicher C, Novacek G, Zauner C, Burghuber M, et al. Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997;**112**:698–706.
140. Wright CL, Riddell RH. Histology of the stomach and duodenum in Crohn's disease. *Am J Surg Pathol* 1998;**22**:383–90.
141. Parente F, Cucino C, Bollani S, Imbesi V, Maconi G, Bonetto S, et al. Focal gastric inflammatory infiltrates in inflammatory bowel diseases: prevalence, immunohistochemical characteristics and diagnostic role. *Am J Gastroenterol* 2000;**95**:705–11.
142. Levine D, Reid B. Endoscopic biopsy technique for acquiring larger mucosal samples. *Gastrointest Endosc* 1991;**37**:332–7.
143. Rozen P, Baratz M, Fefer F, Gilat T. Low incidence of significant dysplasia in a successful endoscopic surveillance program of patients with ulcerative colitis. *Gastroenterology* 1995;**108**:1361–70.
144. Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, et al. Dysplasia in inflammatory bowel disease: Standardized classification with provisional clinical applications. *Hum Pathol* 1983;**14**:931–68.
145. Farmer M, Petras RE, Hunt LE, Janosky JE, Galandiuk S. The importance of diagnostic accuracy in colonic inflammatory bowel disease. *Am J Gastroenterol* 2000;**95**:3184–8.
146. Sheehan AL, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *Br J Surg* 1992;**79**:955–8.
147. Borley NR, Mortensen NJ, Jewell DP, Warren BF. The relationship between inflammatory and serosal connective tissue change in ileal Crohn's disease: evidence for a possible causative link. *J Pathol* 2000;**190**:196–202.
148. Wright R, Truelove SC. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. *Am J Dig Dis* 1964;**11**:847–57.
149. Odze R, Antonioli D, Peppercorn M, Goldman H. Effect of topical 5-amino-salicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. *Am J Surg Pathol* 1993;**17**:869–75.
150. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;**32**:174–8.
151. Bitton A, Peppercorn MA, Antonioli DA, Niles JL, Sha S, Bousvaros A, et al. Clinical, biological and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001;**120**:13–20.
152. Korelitz BJ, Sommers SC. Response to drug therapy in Crohn's disease: Evaluation by rectal biopsy and mucosal cell counts. *J Clin Gastroenterol* 1984;**6**:123–7.
153. D'Haens G, Geboes K, Ponette E, Pennincks F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology* 1997;**112**:1475–81.
154. D'Haens G, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 1999;**116**:1029–34.
155. Nicholls S, Domizio P, Williams CB, Dawnay A, Braegger CP, MacDonald TT, et al. Cyclosporin as initial treatment for Crohn's disease. *Arch Dis Child* 1994;**71**:243–7.
156. Beattie RM, Schiffrin EJ, Donnet-Hughes A, Huggett AC, Domizio P, MacDonald TT, et al. Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease. *Aliment Pharmacol Ther* 1994;**8**:609–15.
157. Breese EJ, Michie CA, Nicholls SW, Murch SH, Williams CB, Domizio P, et al. Tumor necrosis factor alpha producing cells in the intestinal mucosa of children with inflammatory bowel disease. *Gastroenterology* 1994;**106**:1455–66.
158. Fell JME, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, Kitching P, et al. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2000;**14**:281–9.
159. Bataille F, Klebl F, Rümmele P, Straub RH, Wild P, Schölmerich J, et al. Histopathological parameters as predictors for the course of Crohn's disease. *Virchows Arch* 2003;**443**:501–7.

160. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
161. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A): 5–36.
162. Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;**6**: 8–15.
163. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;**49**:777–82.
164. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244–50.
165. Chow DK, Leong RW, Lai LH, Wong GL, Leung WK, Chan FK, et al. Changes in Crohn's disease phenotype over time in the Chinese population: validation of the Montreal classification system. *Inflamm Bowel Dis* 2008;**14**:536–41.
166. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;**119**:895–902.
167. D'Haens G, Baert F, Van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**: 660–7.
168. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006;**130**: 650–6.
169. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. *Scand J Gastroenterol* 2008;**43**(8):948–54.
170. Seksik P, Loftus Jr EV, Beaugerie L, et al. Validation of predictors of 5-year disabling CD in a population-based cohort from Olmsted County, Minnesota, 1983-1996. *Gastroenterology* 2007;**132**:A17.
171. Jones J, Loftus Jr EV, Panaccione R, Chen LS, Peterson S, McConnell J, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008;**6**:1218–24.
172. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;**126**:402–13.
173. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008;**14**: 40–6.
174. Sipponen T, Savilahti E, Karkkainen P, Kolho KL, Nuutinen H, Turunen V, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis* 2008;**14**(10):1392–8.
175. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;**40**: 955–62.
176. Dubinsky MC, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, et al. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008;**6**:1105–11.
177. Armuzzi A, Ahmad T, Ling KL, De Silva A, Cullen S, Van Heel, et al. Genotype-phenotype analysis of the Crohn's disease susceptibility haplotype on chromosome 5q31. *Gut* 2003;**52**: 1133–9.