European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis

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1.0 INTRODUCTION

Crohn's disease (CD(is a lifelong disease arising from an interaction between genetic and environmental factors, but seen predominantly in the developed countries of the world. The precise aetiology is unknown and therefore a causal treatment is not yet available. Within Europe there is a distinct north-south gradient, but the incidence seems to have increased in southern countries in recent years.[1] Many patients live with a considerable symptom burden despite medical treatment in the hope that the aetiology of the disease will shortly be discovered and curative therapies emerge. Although this seems likely to happen at some time in the next decade, 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,[2] Germany,[3] or France), which reach broadly the same conclusions as 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 CD and its dilemmas. As 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 sets out the current European consensus on the diagnosis and management of CD, reached by the European Crohn's and Colitis Organisation (ECCO) at a meeting held in Prague on 24 September 2004. ECCO is a forum for specialists in inflammatory bowel disease (IBD) from 20 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 CD. The second section on current management includes treatment of active disease, maintenance of medically induced remission, and surgery of CD. The third section on special situations in CD includes postoperative recurrence, fistulating disease, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations, and alternative therapy.

The strategy to reach the consensus involved five steps:

(1) Relevant questions on each of 14 separate topics concerning diagnosis and treatment of CD were devised by the chairmen and their working party. The questions were focused on current practice and areas of controversy in the task force topic, sent around to the other chairmen to avoid duplication, and then to all participants in the consensus conference. Participants were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure).[4]

(2) 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 was graded (table 1.1) according to the Oxford Centre for Evidence Based Medicine.[5]

(3) Provisional guideline statements on their topic were then written by the chairmen, based on answers to the questionnaire as well as the literature evidence and were circulated first among the working party and then among the participants.

(4) The working parties then met in Prague on the 23 September 2004 to agree the statements. On 24 September 61 participants gathered under the chairmanship of E F Stange to agree the final version of each guideline statement. Technically this was done by projecting the statements and revising them on screen until a consensus was reached. On one occasion, when the ECCO Board considered that a statement

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was open to misinterpretation and failed accurately to reflect the text, all original participants were asked to vote on new wording by email. 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,[5] based on the level of evidence (table 1.1).

(5) The final document on each topic was written by the chairmen in conjunction with their working party. Consensus guideline statements displayed in boxes 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 S P L Travis and E F Stange 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") are undetermined, such terms reflect clinical decision making (such as when to start immunomodulators). The arbitrariness of some of the definitions is recognised, but the consensus considers it useful to agree 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 CD recruit patients with a Crohn's disease activity index (CDAI) >220. The fallibility of this threshold is illustrated by the high placebo response in recent trials of biological therapy[6] and the trend is now to use a CRP >10 mg/l in conjunction with the CDAI. Remission (see below) is widely accepted as a CDAI <150 and response is increasingly defined as a decrease in CDAI ≥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.[7] This is an inconsistency that needs to be resolved, but until it can be modelled on clinical trial datasets disease activity is generally graded as in table 1.2.

1.1.2 Remission

The criterion used in most clinical trials when selecting CD patients in clinical remission is a CDAI <150.[8] 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 CD. In several studies, a biological index of Brignola <100.[9][10] 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 evaluating the maintenance of remission in CD should last at least 12 months.[8]

Table 1.1 Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine

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; for example, <80% followup)
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	

For details see http://www.cebm.net/levels_of_evidence.asp#refs

Table 1.2 Grading of disease activity in Crohn's disease

Mild	Moderate	Severe
Equivalent to a CDAI of 150–220 For example, 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 For example, intermittent vomiting, or weight loss >10%. Treatment for mild disease ineffective, or tender mass. No overt obstruction. CRP raised above the upperlimit of normal.	Equivalent to a CDAI of >450 For example, cachexia (BMI <18 kg^{-2}), or evidence of obstruction or abscess. Persistent symptoms despite intensive treatment. CRP increased.

1.1.3 Response
Response should be defined by a ΔCDAI ⩾−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 ⩾70 points[11] [12] 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 >150 with an increase of more than 70 points has been proposed.[8] However, if a therapeutic response is defined as a decrease in CDAI ⩾100 points, then the definition would more rationally be a CDAI >150 with an increase of 100 points from baseline. There is no international agreement on this, but future trials on CD 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.

1.1.6 Pattern of relapse
Relapse may be infrequent (⩽1/year), frequent (⩾2 relapses/year), 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 corticosteroids, or who has disease activity despite immunomodulators. As this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions, are preferred, including corticosteroid refractory or corticosteroid dependence.

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

1.1.8 Corticosteroid dependent disease
Patients who are either

(a) unable to reduce corticosteroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within three months of starting corticosteroids, without recurrent active disease, or

(b) who have a relapse within three months of stopping corticosteroids.

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

This definition of corticosteroid dependence requires that the total duration of corticosteroids does not exceed three months before a threshold equivalent to prednisolone 10 mg/day is reached. Patients are still considered corticosteroid dependent if they relapse within three months of stopping corticosteroids. 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 corticosteroids 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 Morphological 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.[13] [14] Endoscopic recurrence is currently evaluated and graded according to the criteria of Rutgeerts et al (0: no lesions; 1: less than five aphthous lesions; 2: more than five 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; 4: diffuse ileal inflammation with larger ulcers, nodules, or narrowing. Hyperaemia and oedema alone are not considered as signs of recurrence).[13]

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.[14]

1.1.12 Localised disease
Intestinal CD affecting <30 cm in extent. This usually applies to an ileocaecal location (<30 cm ileum ± 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 on alternative therapies for comment).

1.1.17 Expert opinion
The term "expert" is used here to refer to the opinion of the specialists in IBD 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 members of the European Society of Pathology (ESP) working group on Digestive Diseases, or European Society of Gastrointestinal and Abdominal Radiology (ESGAR).

2.0 CLINICAL DIAGNOSIS AND IMAGING
CD most frequently presents in late adolescence or early adulthood and is equally distributed between the sexes.[15] 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, as this influences the choice of treatment. The guidance on imaging reflects a gastroenterological perception on

appropriate radiological techniques for patients with CD. Although the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) was not officially involved in the working party, the chairman (W Reinisch) consulted frequently with C Bartram, a founding member of ESGAR, during the process of guideline preparation.

2.1 Clinical features of CD

ECCO statement 2A

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

Chronic diarrhoea is the most common presenting symptom;[16][17] a definition of a decrease in faecal consistency for more than six weeks may be adequate to differentiate this from, self limited infectious diarrhoea.[17][18] Abdominal pain and weight loss are seen in about 70% and 60% respectively of patients before diagnosis. 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).[17] Abnormalities of the musculoskeletal system are the most common extraintestinal manifestations of IBD, encompassing peripheral and axial joints.[19] Extraintestinal manifestations are most common when CD affects the colon (see section 12). Perianal fistulas are present in 10% of patients at the time of diagnosis[20] (see section 9).

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 [EL5, RG D]

CD is a heterogeneous entity comprising a variety of complex phenotypes.[19][21][22] Originally, Dr Burrill Crohn and colleagues described regional ileitis as a chronic inflammatory disease restricted to the terminal ileum in association with intestinal stenoses or fistulas, but not crossing the ileocaecal valve.[23] The original concept has subsequently extended potentially to affect the entire gastrointestinal tract.[24–26] 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 features 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.[17] 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 10%–15% of cases. IBD restricted to the colon that cannot be allocated to CD or UC categories is best termed

colitis unclassified and the term indeterminate colitis confined to operative specimens as originally described.[27] 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, contact with enteric illnesses, medication (including antibiotics and non-steroidal anti-inflammatory drugs), smoking, family history, and history of appendicectomy [EL5, RG D]

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 appendicectomy, and a family history of IBD have been reproduced as risk factors for the onset of CD.[28][29] Retrospective studies on non-steroidal anti-inflammatory drugs as a risk factor for CD are less consistent.[30]

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/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) is recommended [EL5, RG D]. 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. In a patient with a history consistent with CD, additional clinical and laboratory investigations are not necessary [EL5, RG D]

Anaemia and thrombocytosis represent the most common changes in the full blood count in 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 hours.[31–36] 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.[37] Neither of these 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*.[38]

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]

Colonoscopy with multiple biopsy specimens is well established as the first line procedure for diagnosing colitis.[39–41] 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.[39 40 42] The most useful endoscopic features of CD are discontinuous involvement, anal lesions and cobble stoning. Colonoscopy predicts the anatomical severity of CD colitis with a high probability.[43] 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, left colon).[43] When there is severe, active disease, the value of full colonoscopy is limited by a higher risk of bowel perforation[41] and diagnostic errors are more frequent. In these circumstances initial flexible sigmoidoscopy is safer and ileocolonoscopy postponed until the clinical condition improves.[2] The scoring of endoscopic disease activity in CD is reserved for clinical studies.[8] Ileoscopy is superior for the diagnosis of CD of the terminal ileum[44–46] when compared with small bowel radiology, whether performed as follow through (SBFT), intubation (small bowel enema (SBE), enteroclysis), or meal with pneumocolon (SBMP). Enteroscopy with biopsy by a push endoscope is safe and useful procedure for diagnosis of CD in selected patients with suggestive symptoms after failure of conventional radiology.[47] The accuracy of capsule enteroscopy remains to be defined (below).

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

ECCO statement 2G

In a patient with evidence of CD determined by ileocolonoscopy, further investigations are recommended to examine the location and extent of CD in the small bowel irrespective of the endoscopic and histological findings in the terminal ileum [EL1b, RG A]

CD may affect the ileum out of reach of an endoscope, or involve more proximal small bowel (10% of patients.)

Endoscopy and radiology are complementary techniques to define the site and extent of disease, so that optimal therapy can be planned.[46 48]

ECCO statement 2H

Several techniques are used to investigate the small intestine including small bowel follow through, small bowel enema, transabdominal ultrasound, computed tomography (CT)-enteroclysis (-graphy), and magnetic resonance imaging (MRI)-enteroclysis (-graphy). For determination of extent and location of small bowel CD, most centres will perform either a SBE or SBFT, with only some units undertaking CT- or MRI-enteroclysis (-graphy)

Fluoroscopic examinations (SBFT, SBE) are the current standard for assessing the small intestine. These are ubiquitously available and permit a detailed analysis of the extent of diseased mucosal surface. Results of barium studies are, however, strongly influenced by the quality of the examination. Views may be obscured by overlying bowel loops, while recognition of aphthoid ulceration requires good compression. Cross sectional imaging (such as CT) provides additional information on bowel wall thickening, associated changes in vascularity and in the adjacent mesentery, which become more important as the severity of disease increases. The radiation burden from fluoroscopy and CT is appreciable, so alternatives such as ultrasound (US) or MRI should be considered where possible.

Radiographic techniques for imaging the small intestine may be divided into intubation (enteroclysis, CT- enteroclysis and MRI-enteroclysis) and non-intubation studies. Non-intubation examinations include SBFT and oral preparations for MR- or CT-enterography.[49 50] Disagreement persists regarding the optimum fluoroscopic technique for small bowel CD. Placement of a nasojejunal tube is onerous for patients and may result in additional radiation exposure, but the inherent problem of non-intubation strategies is a diminished ability to ensure even distension of the small bowel for accurate assessment of strictures. However, strictures may only be detectable by opacification with distension. Therefore, SBE has been considered the optimum investigation for CD, with a sensitivity of 93% and a specificity of 92% to exclude small bowel disease.[51–53] In routine practice SBFT is simpler and may be preferred; it was superior to SBE for detecting mucosal disease, fistulas, or gastroduodenal involvement in a comparative study in CD,[54 55] but is operator dependent and not as good for strictures. The debate is unlikely to be resolved by wireless capsule enteroscopy or other techniques in the near future.

US is not good at identifying the extent of CD, but its non-ionising character make it suitable for the initial evaluation of a young population, especially for ileal CD. The sensitivity for US is 87%–95% when performed by specialists, which is somewhat less than barium studies,[56–60] but is even more operator dependent. It misses lesions predominantly in the upper GI tract or rectosigmoid. The role of colour, power Doppler and contrast enhanced power Doppler investigation of the bowel wall for defining disease activity remains to be determined.

Intestinal imaging with helical CT-enteroclysis or CT-enterography has improved appreciably, leading to reports that it is complementary or even superior to barium studies for the detection of involved segments.[61 62] MRI has also undergone technical developments that may yet make it the

method of choice complementary to ileocolonoscopy and biopsy for assessing location, extent, and disease activity. Its ability to detect extramural complications (abscess, fistula, sacroiliitis, gall stones, renal calculi) is an added advantage. However, magnetic resonance enteroclysis (MRE) is currently more invasive than SBE, as it involves intravenous, oral and rectal contrast, as well as intravenous antiperistaltic agents. Superior sensitivity and specificity by MRE (95% and 93%) compared with SBE (85% and 77%) has been claimed for the primary diagnosis of CD.[63] MRE can provide useful information about the activity of disease.[64 65]

Leucocyte scintigraphy is safe, non-invasive, and potentially permits assessment of the presence, extent, and activity of inflammation patients who are not taking corticosteroids, but it lacks specificity.[66]

It is premature to recommend any single procedure for imaging of the small bowel. However, the very variety of techniques make it most desirable that clinicians discuss imaging with an appropriate radiologist, so that results can be reviewed in the context of the clinical history.[2 67]

2.3.2 Procedures recommended for establishing the extent of stricturing CD

ECCO statement 2I

Intestinal stenosis is defined by symptoms of obstruction, bowel lumen narrowing, and/or pre-stenotic dilatation. The significance of the extent of luminal narrowing is not clearly defined [EL5, RG D]

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, comparatively short persistent narrowing, whose functional effects may be judged from pre-stenotic dilatation.[68]

ECCO statement 2J

When endoscopic intubation of the intestine is not possible, radiological studies are necessary to determine disease extent and location [EL1a, RG A]. Small bowel enema for small bowel disease and double contrast barium enema for large bowel disease are recommended [EL1c, RG A]. Complementary imaging procedures may be performed, including US, CT, and/or MRI [EL1a, RG A]. Differentiation between inflammatory and fibrostenotic bowel stenosis would be very helpful, but current techniques do not permit an accurate distinction

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Plain film radiography and CT have similar accuracy in identifying small bowel obstruction. Plain film radiography remains the initial method, but the ability to depict the cause of obstruction makes CT an important additional diagnostic tool.[69]

When small bowel stenosis is suspected an enteroclysis examination best distends the bowel to reveal extent and number of strictures. Based on availability, SBE is recommended as investigation of first choice, but MRI-enteroclysis is comparable.[70] The functional significance of a stricture is best illustrated by pre-stenotic dilatation, but it is difficult to

determine the full significance of any narrowing even with intubation studies. Reflux of gas or smooth muscle relaxants can distend narrowed loops. Enteroclysis most reliably differentiates irreversible stenosis from functional spasm. US is helpful in detecting pre-stenotic dilatation in small bowel strictures in severe cases that are candidates for surgery.[71]

If colonoscopy is incomplete because of stricture, then double, or even single contrast barium enema are usually procedures of first choice.[72] CT colonography (CTC) can show the mucosal pattern and show colitis proximal to a stricture, but may not identify all strictures seen on colonoscopy.[73–75]

Differentiation between inflammatory and fibrostenotic strictures is crucial to the choice of therapy, but current techniques are insufficiently accurate. Disease activity at a stricture is inferred from by the presence or absence of ulceration that indicates active inflammation. Contrast enhanced Doppler US may be valuable in determining disease activity within strictures.[76–78] Both CT and MRI illustrate mural changes with disease activity, but MRI is more sensitive.[65 79 80]

2.3.3 Procedures recommended for detecting extramural complications

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ECCO statement 2K

When an extramural complication is suspected, including fistula or abscess, US, CT, and/or MRI are appropriate investigations [EL1c, RG A]

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.[81]

CT and MRI are highly accurate in complicated CD, especially for the detection of fistulas, abscesses, and phlegmons.[82 83] The important advantages of MRI compared with CT include superior tissue contrast, absence of radiation exposure, capability of selecting cross sectional planes (transverse, coronal, sagittal), and higher sensitivity for intestinal and extraintestinal changes in CD.[79] Surgically compared sensitivities for the detection of fistulas and abscesses of 83% and 100% respectively, have been reported for MRI.[84] MRI enteroclysis is good and probably better than US[85] for detecting extramural complications of CD, but fluoroscopic studies are poor value.[63] Laparoscopy may be necessary in selected patients, especially when the differential diagnosis of intestinal tuberculosis is being considered.

2.3.4 Role of gastroduodenoscopy and biopsy in a patient with CD

ECCO statement 2L

In routine practice gastroduodenoscopy is only recommended in patients with upper gastrointestinal symptoms [EL5, RG D]

CD involving the upper gastrointestinal tract is almost invariably accompanied by small or large bowel involvement.[86–88] 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 wireless capsule endoscopy (WCE) in suspected or proven CD

> **ECCO statement 2M**
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> Wireless capsule endoscopy (WCE) represents an advance for small bowel imaging, but large prospective studies are needed to confirm the diagnostic relevance in CD. WCE may be considered in symptomatic patients with suspected small bowel CD in whom a stricture/stenosis has been excluded, endoscopy of terminal ileum is normal or not possible, in whom fluoroscopic or cross sectional imaging have not showed lesions [EL2, RG B]

WCE is a novel method of directly visualising small bowel lesions in patients with IBD that may be missed by traditional endoscopic or radiological procedures. Initial studies suggest that WCE is a superior and more sensitive procedure than SBFT and CT-enteroclysis in establishing the diagnosis and estimating the extent of CD.[89–92] However, CD associated lesions seen at WCE still need more precise definition, because specimens for histological evaluation are not obtained. Large prospective studies are needed to position WCE in a diagnostic algorithm for CD. Contraindications for WCE include gastrointestinal obstruction, strictures or fistulas, pacemakers or other implanted electromedical devices, and swallowing disorders.[93]

2.3.6 Procedures recommended preoperatively

> **ECCO statement 2N**
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> Preoperative imaging should follow strategies used 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 postoperative outcome.[94 95]

3.0 THE HISTOLOGICAL DIAGNOSIS OF CD

During the past 25 years, several elements have influenced the accuracy of the histological diagnosis of CD. The widespread introduction of colonoscopy permitted the analysis of multiple mucosal biopsies from different segment 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 CD were sought from the literature using Medline and Pubmed. As further selection criteria, only those features that achieved moderate reproducibility judged by κ value, or findings that were confirmed by subsequent studies, were considered. The purpose is to propose consensus guidelines for the histological diagnosis of CD. The aspects discussed include: procedures required for a proper diagnosis; features that can be used for the analysis of endoscopic biopsies; features that 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? the role of histology in management? and 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 CD "multiple" biopsies from five sites around the colon (including the rectum) and the ileum should be obtained. Multiple biopsies implies 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 CD.[96–103] Samples are preferably obtained both from areas that 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 CD is suspected. Multiple biopsies are indicated when the patient is 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 before transport [EL5, RG D]

> **ECCO statement 3E**
>
> As 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 permits 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 two and six in different studies.[102] [103] 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 with step sectioning. Confirmation of this finding is needed.[104] 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.[105] 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.[100] [106–110] 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 per cent of the clinicians agree to take two samples from one or two regions in fulminant colitis. Eight per cent do not perform endoscopy in fulminant colitis and 34% would take only one sample. The proposal to use multiple biopsies for the diagnosis of CD is supported by data from the literature.[96] [97] 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 that permit a diagnosis of CD [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 that help to establish a diagnosis of CD, and reported in the literature. They are summarised in table 3.1. The reproducibility of these features, as well as the sensitivity and specificity have 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.

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

Colon
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
Terminal ileum
Architecture
  Villus irregularity
  Crypt architecture irregularity
Epithelial changes
Pseudopyloric gland metaplasia (ulcer associated cell lineage (UACL))
Comparison between different segments
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

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 are present. Crypt irregularity can be either crypt distortion (non-parallel crypts, variable diameter, or cystically dilated crypts), crypt branching, and crypt shortening.[100] The presence of more than two branched crypts in a well orientated biopsy specimen can be regarded as abnormal.[100]

3.2.4 Granulomas

The granuloma in CD 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 CD. Granulomas associated with crypt injury are less reliable features.[111] Non-caseating granulomas, small collections of epithelioid histiocytes, and giant cells, or isolated giant cells can be seen in infectious colitis (granulomas suggest *Mycobacterium sp*, *Chlamydia sp*, *Yersinia pseudotuberculosis*, *Treponema sp*; microgranulomas suggest *Salmonella sp*, *Campylobacter sp*, *Yersinia enterocolitica*; giant cells suggest *Chlamydia sp*) and must not be regarded as evidence for CD.

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 (κ of 0.4 or percentage agreement of at least 80%).[103 104 112 113] 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 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.[96] The patchy nature of the inflammation is only diagnostic in untreated adult patients. Inflammation can become patchy in UC under treatment, and young children (age <10 years) with UC may present with discontinuous inflammation.[114–119]

The presence of one single feature is not regarded as sufficient for a firm diagnosis. For single or multiple endoscopic samples there are no data available as to how many features must be present for a firm diagnosis of CD. For surgical material, it has been suggested that a diagnosis of CCD 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].[109] 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 CD.

Most expert clinicians (91%) and all pathologists agree that the presence of a granuloma and at least one other feature establishes a diagnosis of CD. 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 CD. However, finding a granuloma is not always necessary for a diagnosis of CD. Additional features that have been found to be useful are increased intraepithelial lymphocytes,[96] transmucosal inflammation,[112] focal chronic inflammation without crypt atrophy, focal cryptitis (although reproducibility is poor),[100 120] aphthoid ulcers, disproportionate submucosal inflammation, nerve fibre hyperplasia,[121] 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 CD.

In difficult cases, gastric biopsies might help establish the diagnosis of CD by the presence of granulomas or focally enhanced or focal active gastritis. The latter is characterised by the absence of *Helicobacter pylori* and the presence of a perifoveolar or periglandular cellular infiltrate composed of mononuclear cells ($CD3^+$ T cells and $CD68^+$ cells) and granulocytes. Focal gastritis is not exclusive to CD [EL4, RG C].[122–126]

3.3 Histology and dysplasia-intraepithelial neoplasia
3.3.1 Number of biopsies

> **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. 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]

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 UC [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 UC. 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.[127] These studies on UC have not been replicated in Crohn's colitis. The focal nature of inflammation in Crohn's colitis, the possibility of strictures and prevalence of

segmental resection means that surveillance practice in UC 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, may change the policy of taking biopsies in the future.

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, 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).[128 129]

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 CD.

3.4 Surgery and pathology

ECCO statement 3I

A surgical sample needs a complete macroscopical 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 macroscopical 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.[121 130] The features are

summarised in boxes 3.2 and 3.3. Fat wrapping has a high predictive value for the diagnosis of CD.[131 132]

Box 3.2 Macroscopic features for the diagnosis of Crohn's disease

- Ileal disease*
- Rectum typically spared
- Confluent deep linear ulcers, aphthoid ulcers
- Deep fissures
- Fistulas
- Fat wrapping*
- Skip lesions (segmental disease)
- Cobblestoning
- Thickening of the intestinal wall*
- Strictures

*Typical discriminating features for a diagnosis of Crohn's disease compared with other conditions

Box 3.3 Microscopic features for the diagnosis of Crohn's disease in surgical specimens

- Transmural inflammation*
- Aggregated inflammatory pattern, transmural lymphoid hyperplasia*
- Submucosal thickening (expansion by fibrosis—fibromuscular obliteration and inflammation)
- Fissures
- Sarcoid granuloma (including in lymph nodes)*
- Abnormalities of the enteric nervous system (submucosal nerve fibre hyperplasia and ganglionitis)*
- Relatively unchanged epithelia—mucin preservation (goblet cells often normal)

*Typical discriminating features for a diagnosis of Crohn's disease compared with other conditions

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]

Histological examination is routinely used for the diagnosis of UC and 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.[127]

In contrast with UC, disease activity is not generally assessed by pathologists for CD. This is mainly attributable 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 permit 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 the inflammation seems important for the prevention of the development of cancer,[131–136] but neither have yet been studied in CD. The data available on histology and activity for CD are limited. Several clinical drug trials have shown that medical treatment can change the mucosal histology, promoting healing and normalisation of the mucosa.[135–143] 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.[133] In CD 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.[144]

4.0 CLASSIFICATION OF CROHN'S DISEASE

Disease classification is an important step to provide appropriate tools that enable us to dissect differences in the features and behaviour of CD. Several ways of classifying CD have been used in the past. CD has been classified by disease phenotype (Rome or Vienna classification, modified in Montreal), by disease activity (mostly according to the CDAI), and by response to therapy (mainly corticosteroids: "corticosteroid resistant" or "corticosteroid dependent", above). Some disease causing mutations have been identified in the recent past, classification by genetic markers may be appropriate. Also immunological features such as ASCA or ANCA may look attractive for classifying the disease (immunotyping). The best classification of course would be by cause of disease, which is, however, still obscure.

4.1 General recommendations

> **ECCO statement 4A**
>
> No evidence based recommendation can be made to implement the routine clinical use of: genetic tests (for example, NOD2/CARD15, OCTN1 and 2, DLG5 or combinations); stool markers (for example, calprotectin, lactoferrin); serological markers (for example, ASCA, ANCA, ompC, I2, flagellin antibodies); intestinal permeability testing; or phenotype driven classifications

> **ECCO statement 4B**
>
> 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 Classification by genetic or other markers
Genetic tests are considered to represent any diagnostic test that permits the determination of a particular genetic

constellation. In this capacity, genetic tests may be gene based, but may also comprise protein based tests of gene function. Other tests designed to discriminate or classify CD include serological tests.

NOD2/CARD15 mutations have been clearly associated with susceptibility to CD [EL1a].[145–147] They were further related to particular phenotypes (characterised by ileal and stricturing disease) [EL1a].[148–153] The relative importance of NOD2 mutations differs between white populations and non-white populations (mostly no NOD2 mutations) but also within Europe. It is expected that further disease susceptibility genes will be detected soon [EL2b].[154 155] Genetic tests are not yet implemented in clinical routine strategies because of low individual predictive value and because no preventive or therapeutic strategies based on the genetic findings exist to influence disease. Counselling should be done before any genetic test. Counselling should be performed using an interdisciplinary approach, including human genetics and disease specialists.

Serological tests (ASCA/ANCA) have a high specificity for the diagnosis of CD if the pattern is positive (ASCA⁺/ANCA⁻) [EL2a]. The predictive value is too low for routine clinical use [EL2a].[156–161] Clinical permeability scores using inert macromolecules (such as lactulose, L-rhamnose, or mannitol) show abnormal values in a fraction of patients. They have some predictive value for relapse, but they are not available outside of specialised centres and are of no predictive value for individual patients [EL2a].[162 163]

4.2.2 Classification by phenotype
The Vienna classification was introduced at the World Congresses of Gastroenterology in 1998 and provides the most recent international consensus on CD phenotype.[68] Age at diagnosis (A), disease location (L), and disease behaviour (B) are the three categories for allocating patients. The A and L category seem to be stable during the course of disease, but the B category is not.[164] Patient classification by phenotype has an impact on the choice of medication with regard to disease location and disease behaviour (see also section on therapy). The Vienna Classification is a first step towards standardising this process. At the World Congress of Gastroenterology in Montreal (2005) an update of the Vienna classification was proposed,[165] which includes upper gastrointestinal and perianal modifiers for disease location and behaviour. The possibility of including genetic and serological markers in the classification was examined and the clinical reclassification is in the process of being validated.

4.2.3 Classification by CRP or other indicators of inflammation
Clinical disease activity is habitually determined by CDAI and separates patients with active disease from patients with quiescent disease. The CDAI is heavily weighted towards subjective symptom reports such as diarrhoea, abdominal pain, or general wellbeing. It does not necessarily reflect the inflammatory activity in the gut. Inflammation related markers are therefore detected from the serum or the stool. Therefore more reliable parameters including laboratory tests of inflammation would be useful.

Raised serum CRP is found in patients with endoscopically active CD and low levels of CRP identify patients in stable remission. The CRP in remission may help identify those at a higher risk of relapse [EL2b] (see also section 6.1.2). When 101 patients with CD were followed up prospectively for two years, half had a raised CRP that correlated well with clinical activity. About a third presented with active disease despite a normal CRP and a third had a raised CRP but clinically inactive disease. The likelihood of relapse after two years was

higher for the patients with an increased CRP compared with those with a normal CRP.[166] The GETAID group also prospectively followed up 71 CD patients with medically induced remission and measured laboratory markers (full blood count, CRP, ESR, α_1 antitrypsin, orosomucoid) every six weeks.[161] In total, 38 patients relapsed (defined as a CDAI>150 with an increase of >100 points from baseline) after a median of 31 weeks. Only two laboratory markers were predictive of relapse: CRP (>20 mg/l) and ESR (>15 mm 1st h). Patients with both markers positive had an eightfold increased risk for relapse. The negative predictive value was 97%, suggesting that negative results for both markers could almost certainly rule out relapse in the next six weeks. A further cohort study used biochemical markers to develop a predictive index of relapse.[9] Forty one patients with clinical inactive disease (CDAI <150) for six months were followed up using a range of biochemical markers of inflammation until relapse.[9] A total of 17 of 41 patients relapsed. ESR, α_2 globulin, and α_1 glycoprotein were the best predictors to distinguish relapsers from non-relapsers. The authors concluded that high values predicted relapse in the following one to two years. Very high CRP levels are indicative of bacterial complication (such as an abscess) [EL3]. A variety of other markers (orosomucoid, IL6, sIL2R, intestinal permeability[9 158 163]) may have similar capability.

Stool markers such as calprotectin, lactoferrin, or tumour necrosis factor are related to the extent of ulcerated intestinal surface and to the degree of inflammation These may have a high predictive value for the presence of ileocolonic inflammation and for upcoming clinical relapse.[9 156 161 164] However, properly powered studies are needed to confirm their value in routine practice.

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