Crohn's disease

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Abstract | Crohn's disease is an inflammatory bowel disease that is characterized by chronic inflammation of any part of the gastrointestinal tract, has a progressive and destructive course and is increasing in incidence worldwide. Several factors have been implicated in the cause of Crohn's disease, including a dysregulated immune system, an altered microbiota, genetic susceptibility and environmental factors, but the cause of the disease remains unknown. The onset of the disease at a young age in most cases necessitates prompt but long-term treatment to prevent disease flares and disease progression with intestinal complications. Thus, earlier, more aggressive treatment with biologic therapies or novel small molecules could profoundly change the natural history of the disease and decrease complications and the need for hospitalization and surgery. Although less invasive biomarkers are in development, diagnosis still relies on endoscopy and histological assessment of biopsy specimens. Crohn's disease is a complex disease, and treatment should be personalized to address the underlying pathogenetic mechanism. In the future, disease management might rely on severity scores that incorporate prognostic factors, bowel damage assessment and non-invasive close monitoring of disease activity to reduce the severity of complications.

The global prevalence of inflammatory bowel disease (IBD) has been increasing since 2000, and IBD now affects up to 1 in 200 individuals in Western countries[1]. IBD encompasses two distinct disorders, Crohn's disease (CD) and ulcerative colitis (UC), which differ in pathophysiology, affected parts of the gastrointestinal (GI) tract, symptoms, complications, disease course and management. The cause of CD is still unclear but genetic, immunological and environmental factors contribute to risk of disease onset and progression[2]. CD is characterized by skip intestinal lesions (that is, areas of inflammation interposed between normal-appearing mucosa) anywhere in the GI tract, and involves chronic, relapsing transmural inflammation that can lead to chronic abdominal pain, diarrhoea, obstruction and/or perianal lesions[2]. UC affects only the colon, the lesions are continuous and inflammation is superficial, which can lead to erosions, ulcers and bloody diarrhoea. CD is progressive and destructive — 21–47% of patients also present with systemic, extraintestinal manifestations (EIMs), which strongly affect patients in a multitude of ways, such as their quality of life (QOL) and long-term outcomes, including risk of hospitalization, complications and surgery[2]. Furthermore, half of all patients with CD develop intestinal complications, such as strictures or fistulae, within 10 years of diagnosis. Population-based cohort studies have demonstrated that up to 30% of patients with CD have evidence of bowel damage at diagnosis, and half of these patients require surgery in the 20 years following the diagnosis[3,4]. CD most often presents in patients younger than 30 years, although the incidence is increasing in older individuals. Higher incidence has been reported for Ashkenazi Jews, urban populations and those in northern latitudes, with a peak between the second decade and the fourth decade of life. Many studies have failed to find any sex difference in incidence in Western countries, whereas the incidence of CD is higher in men than in women in Asian populations[5–10].

Currently, mucosal healing is the preferred treatment target, as patients who achieve mucosal healing have improved outcomes, including decreased risk of surgery, lower relapse rates and improved QOL[11]. In the past two decades, the use of anti-inflammatory treatments, such as anti-tumour necrosis factor (anti-TNF) therapy (for example, infliximab, adalimumab and certolizumab), has transformed the management of CD. These drugs are being used earlier in the disease course and are now considered the therapy of choice, especially for patients at high risk of disease progression. Although these targeted biologic therapies are a notable advance in the treatment of CD, the requirement for parenteral administration and the potential for immunogenicity are major drawbacks. Other biologic therapies for CD include the gut-selective monoclonal anti-integrin antibody vedolizumab and an antagonist of IL-12 and IL-23 signalling,

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ustekinumab, for induction therapy and maintaining remission in patients with moderate-to-severe CD[2].

The chronic, unpredictable nature of the disease and its debilitating effect on all aspects of life are major concerns for patients with CD. Health-related QOL (HRQOL), disease activity and disease-associated morbidity will soon be included as measures of treatment outcomes in CD in clinical practice[12,13]. Optimizing care, improving QOL, early disease treatment and predicting bowel damage are milestones that need to be achieved soon and will require a concerted research effort.

In this Primer, we review the epidemiology, pathophysiology, diagnosis and management of CD and the effect of the disease and therapies on patient QOL.

Epidemiology

Incidence and prevalence

The incidence of IBD differs by region, ranging from 0.1 to 58 cases per 100,000 person-years, with the highest incidence reported in North America, northern and western Europe and Oceania[1]. The incidence of CD is 0–20.2 cases per 100,000 person-years in North America and 0.3–12.7 cases per 100,000 person-years in Europe[1]. The highest reported prevalence of CD was in Europe (322 cases per 100,000 persons in Germany) and North America (319 cases per 100,000 persons in Canada)[1].

Since the turn of the twenty-first century, IBD incidence has increased globally, with rapidly increasing incidence reported in newly industrialized countries in Asia, Africa and South America[1]. In China, following urbanization, IBD went from being a rare condition to one that is common and accounts for substantial use of hospital beds[14]. CD incidence follows a south-to-north and east-to-west gradient in mainland China[6]. In Korea, studies reported an incidence of 1.68 cases per 100,000 person-years in 2005, after which it reached a plateau[8,9]. Moreover, the incidence of CD in Asia has increased more rapidly than that of UC[5–8], although the prevalence of IBD is lower than in Western countries. The prevalence of CD in Asian populations has also increased. For example, the prevalence of CD in Taiwan increased from 0.6 cases per 100,000 persons in 2001 to 3.9 cases per 100,000 persons in 2015, and the prevalence of CD in Hong Kong in 2014 was 18.6 cases per 100,000 persons[15,16]. Few studies have reported CD epidemiology data for Latin America and Africa. In both regions, CD incidence and prevalence have been reported as low, although a few studies have reported a high incidence of CD in Brazil[17,18].

The rapid changes in CD epidemiology are a global challenge for disease diagnosis, health care delivery and disease prevention. In newly industrialized countries (such as in Asia), the increasing incidence of CD reflects the influence of the Western lifestyle, particularly diet, urbanization and industrialization, on risk[19]. Furthermore, studies of migrants have shown that individuals who move from low-prevalence to high-prevalence regions are at increased risk of developing CD and that this risk is even more pronounced in the children of immigrants[1].

The incidence of CD has surpassed that of UC in many regions in the West. IBD in children younger than 10 years, and especially those younger than 5 years (very early onset IBD) is becoming more common, and elderly individuals (older than 65 years) with IBD are a rapidly rising population owing to new diagnoses in elderly patients and advancing age of those in whom IBD is diagnosed earlier in adulthood[1]. Owing to a lack of population-based prospective studies to compare CD prevalence and environmental and genetic risk factors for the disease in developing countries with those in developed countries, it is difficult to predict how this increase in incidence will affect phenotypic features of CD in developing countries.

Risk factors

The risk of CD onset and progression is influenced by environmental factors in a genetically susceptible host[1,2] (FIG. 1).

Environmental factors. In Western countries, smoking has been identified as the only modifiable risk factor for CD and doubles the risk of developing CD, although to a greater extent among females and also dependent on age. Smoking is also associated with early disease onset, need for immunosuppression, increased need for surgical intervention and higher rates of postoperative disease recurrence[2]. Several meta-analyses have described a difference in the effect of smoking on CD risk among different ethnicities[20]. Of interest, in Japan, passive smoking is also associated with increased risk of developing CD[20–23].

Gut dysbiosis is a feature of CD, and diet is the most likely environmental factor (of those that have changed in the past decade) to affect the intestinal microbiota. In particular, the host–gut microbiota relationship has been altered by changes in the composition of food and a move from high-fibre, low-fat foods to processed foods that contain food additives[24]. Reduced dietary fibre intake and frequent dietary oscillations between high-fibre and low-fibre foods lead to reduced gut microbiota diversity and are associated with the development of CD[1,2]. As diet has a transient effect on the microbial composition, the involvement of dietary changes in the altered microbial diversity in CD is still the subject of debate. In two prospective studies in Sweden, greater adherence to a Mediterranean diet was associated with a substantially lower risk of later-onset CD[25].

Several studies have shown that the composition of the gut microbiota can change in response to diet[24]. In addition, dietary components can have effects

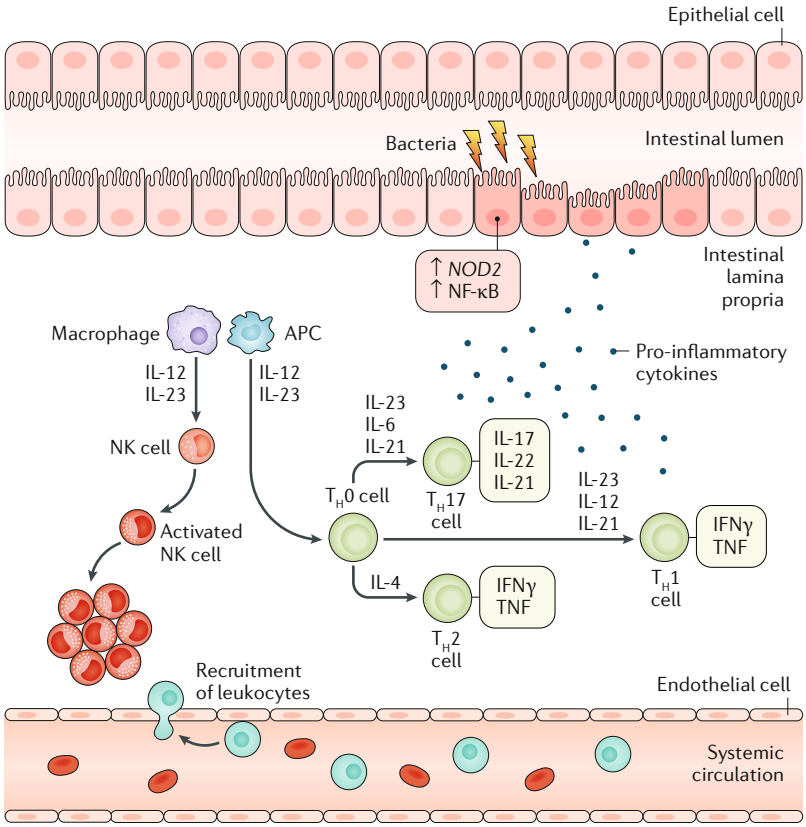

Fig. 1 | **Causes of Crohn's disease.** Intestinal homeostasis is maintained by the equilibrium between the luminal content and the mucosal immune system in the lamina propria. The intestinal epithelium orchestrates this equilibrium because of its mechanical function (as a physical barrier) but also its role in immune responses. Specialized intestinal epithelial cells (IECs) have important roles in intestinal immunity. For example, Paneth cells (not shown) are IECs present at the base of crypts of Lieberkühn and constitutively produce antimicrobial peptides, whereas microfold cells are IECs present in the gut-associated lymphoid tissue (not shown) that sample luminal antigens and present them to cells of the adaptive immune system. After contact with an antigen, antigen-presenting cells (APCs) such as dendritic cells present antigen to T cells and B cells to initiate a controlled inflammatory response. In inflammatory conditions such as Crohn's disease, epithelial barrier dysfunction (owing to, for example, polymorphisms in *NOD2* and nuclear factor-κB (NF-κB) signalling pathway genes) results in the luminal contents entering the lamina propria, leading to dendritic cells activating inflammatory T cell types, such as naive T helper (T_H0) cells, T helper 1 (T_H1) cells, T_H17 cells and T_H2 cells, which produce proinflammatory cytokines, such as IFNγ and tumour necrosis factor (TNF). Furthermore, in response to luminal contents, macrophages produce the proinflammatory cytokines IL-12 and IL-23, which activate natural killer (NK) cells, resulting in perpetuation of the intestinal inflammation with production of proinflammatory cytokines. Luminal contents include dietary components and the gut microbiota. IL-4, IL-6, IL-21 and IL-22 are also produced by T_H0 cells in response to activation of dendritic cells.

on epigenetic modifications and thereby produce long-lasting phenotypic changes[24]. Unravelling the complex interaction between diet and the gut dysbiosis in CD might improve our understanding of the role of diet in CD pathogenesis and lead to the development of novel therapeutic agents.

Antibiotic exposure in childhood increases the risk of developing CD[20]. Furthermore, oral contraceptives, aspirin and NSAIDs have been reported to increase the risk of CD[20,26–28]. Among environmental factors associated with reduced risk of CD, breastfeeding reduce CD risk, albeit inconsistently, and statins are linked to decreased risk[20,29].

Insight into geographical variations, especially related to diet and urbanization, and disease progression is important to prepare the clinical infrastructure and health care resources necessary to mitigate the burden of CD. As potentially relevant environmental factors differ in different populations, selective intervention for disease prevention may need to be targeted towards specific populations. Modifying smoking, judicious use of antibiotics, promoting breastfeeding and appropriate dietary advice might be a reliable approach to reduce CD development and improve long-term outcomes[5]. While better clinical trials are awaited, dietary interventions and newer elimination diets have the potential to better control disease or avoid complications[30]. Future research should focus on identifying environmental factors during the early stages of industrialization that increase disease risk and designing specific interventions that can prevent disease development and improve outcomes in patients with CD (TABLE 1).

Genetic factors. Compared with environmental factors, much more progress has been made in delineating genomic variation that determines disease risk. Familial inheritance of CD is recognized, with concordance rates amongst monozygotic twins that are higher for CD (~50%) than for UC (~15%)[2,31].

Following the seminal discovery in 2001 of coding variation in the intracellular pattern recognition receptor gene *NOD2* (also known as *CARD15*), which is selectively associated with CD risk, genome-wide association studies in more than 70,000 individuals identified more than 200 loci associated with CD risk[32–35]. As in most other diseases, most CD risk loci individually only very modestly increase relative risk (typical odds ratios of 1.1–1.2), and these variants are present mostly in regulatory regions of the genome[35]. Most minor risk loci for CD are shared with a wide range of immunomediated diseases[36]. Importantly, a substantial fraction of aggregate heritable risk is explained by variance at a few loci, including *NOD2* and the autophagy gene *ATG16L1* (both specific for CD), and the IL-23 receptor gene *IL23R* (which increases the risk of CD and UC)[35–37]. The discovery of some variants has identified novel disease mechanisms; for example, *NOD2* c.3019–3020insC and *ATG16L1* p.Thr300Ala have implicated impaired bacterial recognition and autophagy, respectively, in CD pathogenesis[37]. Of note, genome-wide association studies showed that *NOD2* is one of the most important genetic factors associated with the risk of ileal CD[38], and intestinal epithelial cells (IECs) in *Nod2*-deficient mice have impaired bacteria-killing ability, leading to perturbed interactions between the ileal microbiota and mucosal immunity[39].

Remarkably, whereas non-synonymous, coding risk variants in *NOD2*, *ATG16L1* and *IL23R* predominate in white populations, the risk variants of these genes are monomorphic in Asian cohorts[2,40]. In Asians, *TNFSF15* is the predominant risk locus that is selectively associated with CD[17], and its effect size exceeds that of *NOD2* in white populations[41]. A meta-analysis of genome-wide association studies assessed genetic loci associated with IBD in East Asian populations and identified new loci involved in B cell function[42]. By contrast, the large

Table 1 | **Environmental risk factors for Crohn's disease**

Environmental factor	Association	Refs
Smoking	Strong positive association with disease onset and worse disease course	2,7
Appendectomy	Positive association with disease onset and no association with disease course	2,7
Low dietary vitamin D	Positive association with disease onset and course	8,9
Oral contraceptive use	Strong positive association with disease onset and no association with disease course	2
Postmenopausal hormone use	No association with disease onset and no association with disease course	2,7
NSAID use	Positive association with disease onset and strong positive association with disease course	2,7
Antibiotic use	Positive association with disease onset and with disease course	2,7
Depression and psychosocial stress	Positive association with disease onset and no association with disease course	2,7,10
Low dietary fibre	Negative association with disease onset and no association with disease course	8,9
High dietary fat	No association with disease onset or with disease course	8,9
High dietary protein	No association with disease onset or with disease course	8,9

number of CD risk loci with individually small contributions seem to be better correlated between ethnicities[40]. Of note, this transethnic association study showed that most risk loci are shared among diverse ancestry groups, with the few that affect population specificity related to heterogeneity in risk allele frequency (*NOD2*) or effect size (*TNFSF15* and *TNFSF8*)[41]. Moreover, patients with early-onset IBD have mutations in IL-10 receptor genes that show highly penetrant, Mendelian-like inheritance[43].

As only 13.1% of disease heritability is explained by genetic factors[2,44], non-genetic environmental factors and epigenetic factors also have important effects on CD risk. Moreover, genetic variation alone does not explain disease variance and phenotypes, including age at diagnosis, location and complications[45]. However, data from the largest genotype–phenotype study in patients with IBD showed a possible distinction between ileal CD, colonic CD and UC on the basis of genetic risk factors[45]. This study showed that *NOD2* variants are associated only with disease location in patients with CD but not with stricturing disease, suggesting that location is patient specific (that is, influenced by genetic factors), whereas disease behaviour, including complications, is a marker of disease progression[45].

Mechanisms/pathophysiology

Inflammation of the GI tract in CD involves impaired intestinal barrier function and dysregulation of innate and adaptive immune responses and possibly also the gut microbiota.

Intestinal barrier function

The intestinal barrier, comprising IECs, innate immune cells, intraepithelial lymphocytes (IELs) and the mucus layer, is the first physical and chemical barrier encountered by intestinal bacteria, pathogens and food antigens[46] and is in constant homeostasis with the intestinal luminal contents. A defect in any of these barrier components can lead to inflammation. Susceptibility polymorphisms in genes encoding junctional proteins, such as E-cadherin, guanine nucleotide-binding protein subunit-α12 and zonula occludens 1 in IECs, defective production of antimicrobial peptides by innate immune cells and IELs, and altered expression of junctional proteins, such as E-cadherin, β-catenin and claudins, by IECs result in the increased permeability that is a feature of IBD[47,48]. Specifically, reduced expression of the sealing tight junction proteins claudin 5 and claudin 8 and increased expression of the pore-forming claudin 5 in IECs occur in active CD[47,48].

An emerging organizing principle of the mucosal immune response relates to the single layer of IECs. The term 'intestinal barrier' has been used to refer to the mucus layer or the underlying mucosal immune system[49]. CD-associated polymorphisms in several genes, such as *NOD2*, *ATG16L1*, *IRGM* and *LRRK2*, manifest themselves as abnormalities in the secretory activity of Paneth cells, specialized IECs that are present at the base of the crypts of Lieberkühn in the small intestine[50–53]. Endoplasmic reticulum stress within IECs, which can be triggered by a wide range of environmental cues, can elicit a pathological unfolded protein response (UPR) and initiate intestinal inflammation[54–56]. *ATG16L1* polymorphisms (such as p.Thr300Ala) in IECs set the threshold for tolerable endoplasmic reticulum stress by determining the activation level of the UPR sensor inositol-requiring enzyme 1α (IRE1α); hyperactivation of IRE1α can trigger spontaneous ileitis in mice, which phenocopies key features of CD[56]. STAT3 signalling and nuclear factor-κB (NF-κB) signalling in IECs are similarly important, and defects in these two pathways favour the development of colitis[57]. Inhibitor of NF-κB kinase-α (IKKα) phosphorylates ATG16L1 and thereby prevents its degradation, in the absence of which IRE1α accumulates and relays a pathological UPR, which highlights one of many levels of cross-regulation of these key pathways[58].

IELs are predominantly antigen-experienced T cells that reside within the gut epithelium and have a crucial role in maintaining gut homeostasis, although their role in CD pathogenesis is poorly understood and some studies are in contrast with its role in maintaining gut homeostasis and have shown a proinflammatory role of IELs in CD. CD8αα-expressing $CD4^+$ IELs are a subtype of $CD4^+$ IELs that modulate the activity of other immune cells by, among other mechanisms, producing the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGFβ), but also directly respond to epithelial injury or microbial infection in their role as cytotoxic T lymphocytes[59]. Recently, increased production of IL-17A, IFNγ and TNF was identified in IELs from patients with CD[60]. Consequently, IEL dysfunction, such as excessive activity of cytotoxic T lymphocytes or pathological reduction in their anti-inflammatory activity, might contribute to CD[61].

The immune response

IECs communicate with innate and adaptive immune cells by multiple mediators; for example, endoplasmic reticulum stress upregulates NKG2D ligands and

activates natural killer cells and group 1 innate lymphoid cells (ILC1s)[62], which is notable, as NKG2D blockade may be effective in inducing remission in CD[63]. Conversely, IECs receive crucial signals from various leukocytes, including the cytokines IL-22 and IL-17 derived from IL-17-producing T helper cells (T_H17 cells), ILC3s and γδ T cells, which promote IEC regeneration and barrier fortification[64,65].

Innate immunity. Neutrophils, dendritic cells, monocytes, macrophages and ILCs are components of the innate immune response. Mutations in various genes, such as *NOD2*, *ATG16L1*, *LRRK2*, *XBP1* and *IRGM*, lead to alterations in Paneth cell survival and function, including dysregulated secretion of antimicrobial proteins[66]. NOD-like receptors are innate immune proteins that can initiate NF-κB-dependent and mitogen-activated protein kinase-dependent gene transcription, resulting in the production of protective anti-inflammatory cytokines[64,65]. Dendritic cells in inflammatory states express TLR2, TLR4 and co-stimulatory receptors; signalling through these molecules results in the production of proinflammatory cytokines. In homeostatic conditions, IECs produce TGFβ, which promotes the production of the anti-inflammatory cytokine IL-10 by dendritic cells to maintain tolerance. Thus, dendritic cells control crosstalk between innate and adaptive immunity to maintain homeostasis[46]. Neutrophils have important functions in maintaining gut homeostasis and in the inflammatory process. Initially in IBD, neutrophils phagocytose pathogenic microorganisms to maintain homeostasis, but later their subsequent accumulation within the gut epithelium compromises epithelial barrier function and leads to the production of inflammatory mediators that perpetuate gut inflammation[67]. Macrophages in the healthy human gut mucosa seem to be in a tolerant state and control tissue remodelling through the clearance of apoptotic or senescent cells[67].

Current effective CD therapies act to block inflammatory mediator production and signalling and, therefore, are perceived as inhibiting unrestrained inflammation. However, several lines of evidence suggest that defects in phagocytic function and an immunodeficiency element are also important in CD pathogenesis[68]. Impaired neutrophil NADPH oxidase activity has been described in very early onset CD[69]. CD-associated risk variants of *NOD2* and *ATG16L1* are hypomorphic, and NOD2 and ATG16L1 functionally and, in some contexts, also physically interact to promote autophagy in dendritic cells, macrophages and neutrophils, thereby increasing their antimicrobial function[70,71]. Furthermore, neutrophil inflammatory responses to killed *Escherichia coli* are reduced in patients with CD but not in those with UC or rheumatoid arthritis, supporting the view that neutrophil antimicrobial defences are defective in CD[72].

ILCs have an important role in the maintenance of gut homeostasis by producing cytokines that bridge the innate and adaptive immune systems. ILCs are classified into natural killer cells, ILC1s, ILC2s, ILC3s and lymphoid tissue inducer cells. The increased abundance of ILC1s and ILC2s in patients indicates a potential role for these cells in IBD pathogenesis[73]. Inflamed ileum and colon of patients with CD contain increased numbers of ILC3s, and ILC1s are more abundant in the ileum of patients with CD than in patients without ileal inflammation[73]. Furthermore, the inflamed areas contain an increased abundance of IFNγ-producing ILC1s at the expense of ILC3s (which produce the anti-inflammatory cytokines IL-17 and IL-22), suggesting that increased ILC3-to-ILC1 plasticity may be involved in CD pathogenesis. The proinflammatory cytokine IL-12 seems to drive ILC1 differentiation from ILC3s[74]. Importantly, the damaged epithelium activates ILCs to restore epithelial barrier function[75].

Adaptive immunity. Most lymphocytes are activated in the gut-associated lymphoid tissue and are recruited to sites of inflammation. Integrins, such as αLβ2, α4β1, α4β7 and αEβ7 integrins, on the surface of leukocytes are pivotal in the 'rolling phase' of leukocyte extravasation, as they enable leukocytes to bind to cellular adhesion molecules on the surface of endothelial cells. Studies in mice established that the binding of the adhesion molecule MADCAM1 on intestinal endothelial cells to α4β7 integrin on T cells is a crucial intestinal homing mechanism, with this gut tropism imprinted on T cells by Peyer's patch dendritic cells[76,77]. Indeed, a monoclonal anti-α4β7 integrin antibody[78] and an anti-α4 integrin antibody that also blocks α4β1 integrin[79] are efficacious in treating CD.

Several studies have reported a persistent T cell immune activation in IBD[67]. CD results from excessive T helper 1 (T_H1) and T_H17 cell responses to proinflammatory cytokines, such as IL-12, IL-18 and IL-23, which are produced by antigen-presenting cells and macrophages[68]. In turn, T_H1 and T_H17 cells secrete the proinflammatory cytokines IL-17, IFNγ and TNF, which perpetuate inflammation by stimulating production of TNF, IL-1, IL-6, IL-8, IL-12 and IL-18 by other cells, such as macrophages, endothelial cells and monocytes[68].

IL-12 and IL-23 are heterodimeric cytokines that share the p40 subunit while pairing with p35 and p19 subunits, respectively. They are produced by innate immune cells (such as macrophages, dendritic cells and possibly neutrophils) and have emerged as central drivers of intestinal inflammation and major mediators of inflammation in IBD. Studies in T cell-dependent and innate immune cell-driven models of experimental colitis demonstrate that IL-23 is especially important. IL-23 signals through a heterodimeric receptor consisting of IL-23R and IL-12Rβ1 to activate JAK2–STAT3 signalling and is expressed by αβ T cells, γδ T cells and ILC3s. A monoclonal anti-p40 antibody (targeting both IL-12 and IL-23) is effective in CD treatment, and several anti-p19 antibodies (which specifically target IL-23) showed efficacy in CD treatment in phase II trials[79]. Whereas T_H17 cells in the intestine (which contribute to mucosal homeostasis by producing barrier-protective IL-17 and IL-22) develop independently of IL-23, IL-23 activates pathogenic $CD4^+$ lymphocytes that produce granulocyte–macrophage colony-stimulating factor and IFNγ and can also inhibit intestinal regulatory T cells (T_{reg} cells) in experimental model systems[68]. Polymorphisms in the coding sequence of *IL23R* that

are associated with CD and UC risk are hypermorphic[80], suggesting that this immune pathway is indeed close to the core immunogenetic mechanism of both diseases[81].

The activity of effector T cells is regulated by T_{reg} cells, a suppressive subset of $CD4^+$ T cells that have a role in maintaining immune homeostasis in the gut and other tissues and organs. Mucosal effector T cells from patients with IBD may be resistant or less responsive to T_{reg} cell-mediated suppression[82]. IL-10 production by T_{reg} cells is essential to prevent intestinal inflammation in mice[43]. Of note, mutations in the genes encoding IL-10 and IL-10 receptor have been associated with very early onset IBD[43].

Microbial dysbiosis

In the past 10 years, gut dysbiosis (pathological alteration of the gut microbial composition) has been extensively investigated in patients with IBD. However, no microbiota composition or marker microorganisms that are specific to CD have been identified.

Gut bacterial composition. The gut microbiota has been evaluated in different intestinal conditions, including IBD and irritable bowel syndrome (IBS)[83], and both overlaps and differences in composition were found. Gut microbial dysbiosis promotes intestinal inflammation in experimental model systems[84]. A reduced representation of Firmicutes and Bacteroidetes and an overrepresentation of enterobacteria in the microbiota of patients with CD has been described[67,85]. Moreover, adherent–invasive *E. coli* and *Faecalibacterium prausnitzii* have been associated with promotion of CD (by overcolonization of epithelial cells) and protection against CD (by butyrate production), respectively[86–88]. Adherent–invasive *E. coli* can cause granulomatous colitis in boxer dogs, which can be cured by antibiotic treatment[89]. No robust clinical trial data are yet available for the efficacy of faecal microbiota transplantation in treating CD. Studies have identified specific taxa whose abundance is altered (lowered or increased) in patients with poor prognosis, no therapeutic response to conventional or biologic treatments, poor lifestyle or likelihood of relapse after surgery or in relationship to short-chain fatty acid production through different metabolic pathways[90]. Furthermore, patients with CD who have active disease showed an altered microbial community compared with healthy individuals or patients with inactive CD, with enrichment in *Escherichia* spp. and a decrease in abundance of Firmicutes, probably linked to increased vascular and paracellular permeability[91]. Of note, *Enterococcus* spp., *Escherichia* spp., *Fusobacterium* spp., *Streptococcus* spp. and *Veillonella* spp. have been identified as promising, specific, cross-disease markers for bile duct obstruction and GI inflammation, highlighting their role in concomitant biliary disease, such as primary sclerosing cholangitis[92].

Gut viral and fungal composition. In the past 5 years, research into the role of the gut viral community in IBD has increased. Several studies have shown a role of the gut viral community and fungal microbiota in IBD pathogenesis[93]. Of interest, *Caudovirales* bacteriophage sequences have been detected in intestinal washes and biopsy tissues of paediatric patients with CD and might be a potential biomarker of early-onset CD[93]. A meta-analysis showed a lower diversity of both the viral community and the microbiota (but variability between samples was higher) in patients with CD compared with healthy individuals, with increased abundance of *Synechococcus* phage S CBS1 and viruses of the family *Retroviridae* in CD samples[94]. Moreover, in a Japanese cohort, the overall structure of the fungal microbiota in patients with CD seemed to differ completely from that of healthy individuals or patients with UC, with an abundance of *Candida* spp. in patients with CD compared with healthy individuals[95].

Diagnosis, screening and prevention

Although the natural history of CD is well understood, diagnosis can be challenging, as it is not based on a single specific finding and there are no pathognomonic features. Instead, diagnosis requires a complete assessment based on clinical history, physical examination and complementary diagnostic tests, such as assays for serological and faecal biomarkers, cross-sectional and endoscopic imaging, and histological evaluation of biopsy specimens[96,97].

Natural history

Disease phenotype. CD has different presentations or phenotypes: stricturing disease due to fibrosis; penetrating disease due to fistulas between the gut and other structures; disease lacking these features, which is termed inflammatory or non-stricturing, non-penetrating disease; and stricturing, penetrating disease. Disease phenotype can change from inflammatory disease to stricturing, penetrating disease, as repeated cycles of inflammation can lead to bowel damage.

Disease location. Disease location usually remains stable over time. Approximately one third of patients with CD present with large-bowel disease, one third with ileocolonic disease and one third with small-bowel disease. The prevalence of upper GI tract involvement in CD differs substantially among studies. Upper GI tract involvement was initially considered of low prevalence (0.3–5%), but higher prevalence (30–75%) has been reported in the past two decades[98,99]. 'Upper GI tract involvement' refers to involvement of the oesophagus, stomach, duodenum and jejunum either in isolation or together with other locations[98,99].

Up to one third of patients have evidence of stricturing or penetrating intestinal complications at diagnosis, and half of all patients experience an intestinal complication in the 20 years after diagnosis[100]. A substantial proportion of patients (40%) have bowel damage within 1 year of diagnosis (when the first cross-sectional imaging analysis is done). Having bowel damage at diagnosis is associated with worse outcomes, including high rates of surgery and hospitalization[101]. These findings confirm the need to stratify patients at early stages of the disease on the basis of the risk of progression[101]. Treatment with immunomodulators or TNF antagonists within the first 2 years of CD diagnosis reduces the risk of developing bowel strictures when compared with starting treatment

with these drugs more than 2 years after diagnosis. Furthermore, early immunomodulator treatment is associated with reduced risk of intestinal surgery, perianal surgery and any complication[102]. The cumulative risk of developing perianal disease during the course of CD is 30% at 1 year after diagnosis[103].

Female sex and EIMs are associated with increased risk of perianal lesions other than fistulas, whereas older age at diagnosis is associated with a slightly decreased risk of these lesions[104]. Data from a population-based inception cohort of patients with CD indicated a cumulative incidence of perianal or rectovaginal fistulas of 24% at 30–40 years after a CD diagnosis and a decreased cumulative incidence of perianal or rectovaginal fistulas and proctectomy in the biologic era compared with the prebiologic era. The decreased incidence might be explained by a change in the treatment paradigm from a conventional step-up (escalation-as-needed) approach to a top-down (intense-therapy-first) approach[105].

CD is characterized by periods of remission interspersed between flares of intestinal inflammation. Disease flares occur randomly and are mostly unpredictable. Stable and prolonged endoscopic remission occurs in 10% of patients[106]. Up to 50% of patients require intestinal resection within 10 years of a CD diagnosis owing to intestinal complications[12].

Symptoms. Symptoms can be insidious, can be nonspecific and can depend on disease location and severity, and some patients may have symptoms for years before a CD diagnosis[107]. Diarrhoea and abdominal pain are the cardinal symptoms reported by patients with CD[97]. Other symptoms include fatigue, weight loss, fever, anaemia and recurrent fistulas or other perianal findings (ulcers or fissures). Bowel obstructions in patients with stricturing disease result in lack of bowel movements, which can lead to hyperactive bowel sounds, nausea and vomiting. Fistulas or abscesses can be a manifestation of penetrating disease[103,104]. When an abscess is present, patients can have systemic symptoms, such as fever and chills. The symptoms resulting from fistulas depend on the location of the fistula: diarrhoea in the case of enteroenteric fistulas, urinary tract infections in the case of enterovesicular (between the intestine and the bladder) or enterouretheral fistulas, passage of stool to the vagina in the case of enterovaginal fistulas or drainage of stomach or intestinal contents from the skin in the case of enterocutaneous fistula. Symptoms are similar in patients with early-onset CD and in patients with late-onset CD, but there are some differences. For example, EIMs are less common, the disease is less progressive and a family history is less common in patients with late-onset CD than in patients with early-onset CD.

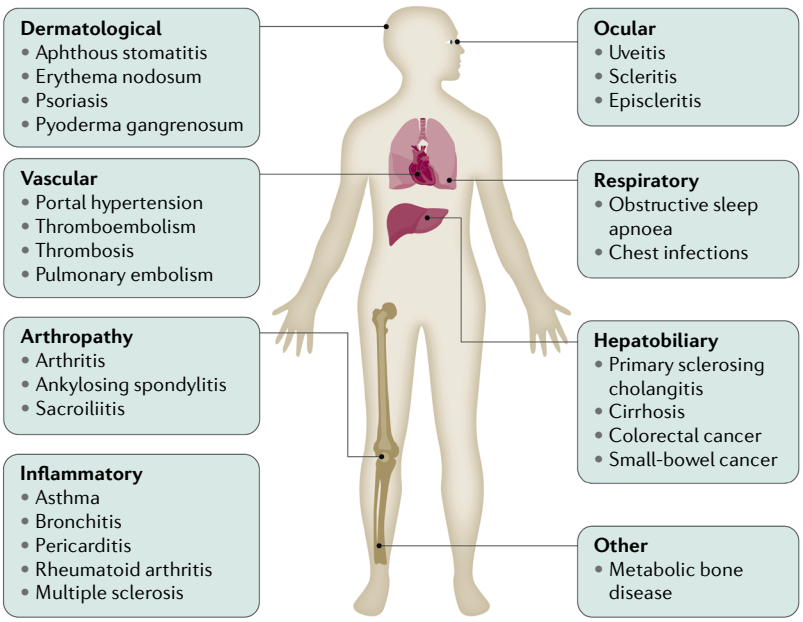

Fig. 2 | **Extraintestinal manifestations and complications in Crohn's disease.** Crohn's disease is associated with various manifestations and complications beyond those in the affected areas of the gastrointestinal tract. Many of these conditions result from immune system dysfunction, including inflammatory conditions in the skin, eyes, joints and respiratory, musculoskeletal and nervous systems. Furthermore, vascular and metabolic dysfunction and cancer can also occur in Crohn's disease.

Extraintestinal manifestations. Overall, EIMs are present in 43% of patients with CD, and can affect multiple body systems, including musculoskeletal (axial and peripheral arthropathy, arthritis and ankylosing spondylitis), oral (aphthous stomatitis), ocular (uveitis, scleritis and episcleritis), dermatological (pyoderma gangrenosum, psoriasis and erythema nodosum) and hepatobiliary (primary sclerosing cholangitis) systems[108] (FIG. 2). These EIMs may be present even before GI symptoms appear, and the presence and/or persistence of some EIMs is linked to intestinal disease activity. For example, axial arthropathy (including ankylosing spondylitis and sacroiliitis) and erythema nodosum track intestinal disease activity[104] and typically disappear when luminal inflammation is successfully treated. Conversely, peripheral arthropathy (type 2 polyarticular), the symptoms of which are often migratory, and pyoderma gangrenosum are usually independent of disease activity (except for type 1 pauciarticular arthropathy) and can persist after the luminal inflammation is treated[109]. Primary sclerosing cholangitis is more common in patients with UC than in patients with CD[104]. However, because of the progressive nature of primary sclerosing cholangitis, further extraintestinal complications can occur, including cirrhosis, portal hypertension, cholangiocarcinoma and colon cancer[104]. Patients with CD have an increased risk of developing colorectal cancer and small-bowel cancers compared with the general population[109].

A slightly increased risk of lymphoma, despite treatment such as with immunosuppressive drugs, was reported in a meta-analysis of population-based studies[104]. Overall mortality is slightly increased in patients with CD (standardized mortality ratio 1.4)[110]. Additional EIMs have also been described, such as metabolic bone disease and thromboembolic diseases[98,104], including threefold increased risk of deep venous thrombosis and pulmonary embolism compared with the general population[108].

EIMs can also result from treatment of CD; for example, one third of patients with CD develop steroid dependency, with surgery required in one third of these

patients after initiation of steroid therapy because of a lack of response to treatment[107]. Various inflammatory diseases, such as asthma, bronchitis, pericarditis, psoriasis, rheumatoid arthritis and multiple sclerosis, are associated with CD[110].

Imaging modalities

Endoscopic imaging. Ileocolonoscopy remains the gold standard for the diagnosis of CD and allows the collection of tissue samples for histological evaluation[111]. Endoscopic findings for a diagnosis of CD include a patchy distribution of inflammation and skip lesions. Macroscopic lesions found in CD are aphthous erosions (ulcers with diameter less than 5 mm) or ulcers that tend to be longitudinal (with diameter greater than 5 mm) with a cobble-stone appearance. Ulcers can be superficial or deep, if they erode the muscularis propria; this feature is one of the criteria of disease severity. Rectal involvement and circumferential continuous inflammation are less common in CD than in UC.

Current guidelines recommend that small-bowel capsule endoscopy (SBCE) should be reserved for patients where there is high suspicion of CD despite previous negative ileocolonoscopy and radiological findings[97]. SBCE uses a disposable swallowed capsule-shaped tool that wirelessly transmits images to a data recorder that is worn by the patient[111], and is a sensitive tool to detect mucosal abnormalities, such as aphthous erosions or ulcers in the small bowel[112]. The diagnostic yield of SBCE for suspected or established CD is higher than that for ileocolonoscopy (47% versus 25%; $P = 0.009$) and CT enterography (CTE; 68% versus 21%; $P < 0.00001$), and SBCE had a high negative predictive value[113]. There is a risk of capsule retention when obstructive symptoms or stenosis are present (13% in patients with established CD and 1.6% in patients with suspected CD)[114]. In these situations, dedicated small-bowel cross-sectional imaging modalities are recommended as the first-line assessment method[115]. Device-assisted enteroscopy is an invasive, time-consuming method that is recommended only in selected patients for whom histological diagnosis is needed or when endoscopic therapy is indicated[116]. Increased costs and the complexity of device-assisted enteroscopy limit its use as a first-line tool in diagnosis of small-bowel CD[97].

Cross-sectional imaging. Cross-sectional imaging (such as bowel ultrasonography (BUS), CTE and MRI enterography (MRE)) is important for fully assessing disease extent and the presence of inflammatory complications (such as stenosis, fistulas and abscesses) owing to the transmural nature of CD[100]. BUS, CTE and MRE have comparable (and high) accuracy for both CD diagnosis and detecting complications in patients with CD[117]. As CTE requires the use of oral or intravenous contrast agents, exposure to radiation is the major limitation of this method[118]. CTE has greater than 80% sensitivity and specificity for CD diagnosis[119] and high sensitivity and specificity for diagnosis of fistulas and for detecting CD-related stenosis[120]. MRE has 89% sensitivity and 94% specificity for the diagnosis of stenosis[121,122]. Pelvic MRE is the imaging modality of choice for the evaluation of perianal fistulas and adjacent abscesses[123]. Although BUS has some limitations, it has emerged as a reliable, non-invasive, radiation-free tool for accurate evaluation of the intestinal wall and extraluminal manifestations[117]. Detection of bowel wall thickening of more than 3 mm by BUS results in high sensitivity and specificity in diagnosing CD (88–100% when enhancement, localization, fistulas and abscesses are considered)[121]. Furthermore, BUS also has high sensitivity and specificity for the detection of extraluminal complications, such as fistulizing and stenotic lesions, and abscesses[122].

Histology

Histological examination of endoscopic biopsy samples or resection specimens is the gold standard for confirming a CD diagnosis and for differential diagnosis (of UC and other non-IBD-related forms of colitis, especially infectious forms). Although there are no histological features that are specific for CD, typical microscopic features that allow a CD diagnosis include focal (discontinuous) chronic inflammation, focal crypt irregularity (discontinuous crypt distortion), granulomas (not related to crypt injury) and irregular villous architecture (in the terminal ileum)[114]. The pathologist in an IBD multidisciplinary team has an important role in increasing accuracy in the CD diagnosis. Even in cases of non-specific histological findings, the presence of clinical, endoscopic and imaging findings allows a tentative diagnosis of CD to be made.

Clinical disease activity indexes

The Crohn's Disease Activity Index (CDAI) is a clinical activity index that was developed in 1976 and is used to quantify the symptoms in patients with CD by assigning a weighted score for eight clinical or laboratory variables, including general well-being, loose stool, abdominal pain, presence of abdominal mass, weight change, low haematocrit and opiate use for diarrhoea. The CDAI is solely applied in clinical trials to define response to treatment or disease remission because 50% of patients in clinical remission have endoscopic and/or C-reactive protein (CRP) evidence of residual, active CD, whereas other patients have normal endoscopic findings and CRP levels despite having symptoms[124]. The Harvey–Bradshaw index (HBI) is a simplified Crohn's disease activity index that was developed in 1980, and includes only clinical parameters, removing the requirement for laboratory analysis. Neither index includes endoscopic and radiological assessment and therefore they are solely used to monitor clinical activity. Inclusion of inflammatory markers in the HBI or the CDAI in the future might add prognostic value to these two indexes. Of note, CDAI and HBI scores were positively correlated in the PRECiSE 1 and PRECiSE 2 trials[124]. The HBI may be more appropriate than the CDAI in some clinical trials and even in routine practice because it is easier to calculate and is less subject to recall bias[125].

Biomarkers

Biomarkers are useful non-invasive tools that give additional information in the management of patients with CD. Data are still lacking regarding their utility in CD

diagnosis. However, biomarkers might help clinicians in early decisions and interventions characterizing the severity and prognosis of the disease. Moreover, biomarkers might have a role in defining response to treatment and in predicting relapses in the postoperative CD.

Serological markers. Autoantibodies, such as perinuclear antineutrophil cytoplasmic antibodies (pANCAs), and antimicrobial antibodies, such as anti-*Saccharomyces cerevisiae* antibodies (ASCAs), anti-*Pseudomonas fluorescens*-associated sequence I2 antibodies, anti-outer membrane porin C antibodies and anti-CBir1 antibodies, are useful biomarkers for CD diagnosis[126]. Other circulating antibodies against glycan epitopes of the bacterial cell wall, such as anti-mannobioside carbohydrate antibodies, anti-laminaribioside carbohydrate antibodies, anti-chitobioside carbohydrate antibodies and anti-laminarin antibodies, are also potentially beneficial for CD diagnosis[127,128].

ASCA is the most well-known serological marker in commercial use for CD diagnosis. The ASCA-positive rate is 60–70% in CD, 10–15% in UC and less than 5% in patients with non-IBD colitis[126]. pANCA is detected in 10–15% of CD cases, 60–70% of UC cases and less than 5% of non-IBD colitis cases[126]. Moreover, patients with CD who are pANCA-positive usually have a clinical phenotype resembling that of UC[11]. Despite the widespread use of these antibodies, usually to differentiate between CD and UC, their practical clinical utility in general diagnosis of CD is limited and genetic or serological testing is currently not recommended for routine diagnosis of CD[129].

CRP is a surrogate serological marker of non-specific acute inflammation in CD[130]. CRP is mainly synthesized by hepatocytes in response to proinflammatory cytokines, such as TNF, IL-1β and IL-6, and is potentially helpful to monitor disease activity in patients with CD[97,131]. Of note, one third of patients with CD have normal CRP levels despite active disease and one third have increased CRP levels despite clinically inactive disease[131]. Furthermore, the value of CRP in predicting clinical disease course is not well established[132–135].

Faecal calprotectin. Faecal biomarkers are potential non-invasive tools to aid in differential diagnosis, especially of inflammatory colitis, or as indicators of CD disease activity[131,136]. Calprotectin is a calcium-containing antimicrobial protein complex that makes up 60% of the cytosolic protein in neutrophils (and lower levels in monocytes and macrophages), and is released during acute and chronic inflammation of the GI tract wall[137]. Faecal calprotectin has high sensitivity and specificity in the diagnosis of CD[136,138]. Faecal calprotectin also has high sensitivity and negative predictive value in differential diagnosis of IBD from IBS in patients in whom there is clinical suspicion of CD, is useful in clinical practice as a screening test indicating the need for further investigation, and reduces the requirement for endoscopic diagnosis in adults by 67% and in children and teenagers by 35%[139]. Despite the lack of validated cut-off values, faecal calprotectin, besides C-reactive protein, is considered the standard test for assessing disease activity in CD and showed utility especially in monitoring disease activity, relapse, response to therapy and patient-reported outcomes in patients with CD[136]. Faecal calprotectin also has a crucial role in a treat-to-target strategy, as in the CALM study, where faecal calprotectin levels were among the treatment failure criteria used for dose escalations in early CD. To date, there is no consensus on a specific cut-off value.

In the STORI trial, patients relapsing after stopping infliximab therapy had increased faecal calprotectin levels 4–6 months in advance of relapse[140]. Furthermore, in an Italian prospective study, a faecal calprotectin value greater than 200 μg/g within 3 months of surgery showed 63% sensitivity and 75% specificity in predicting endoscopic disease recurrence at 1 year[141].

Novel potential non-invasive biomarkers

As intestinal dysbiosis is implicated in the pathogenesis of CD, several studies have evaluated the role of faecal and serum microbial markers for diagnosis of CD. In a multicentre prospective study of an Asian population (95 patients with CD, 81 patients with UC, 65 patients with IBS and 105 healthy volunteers), a combination of substantially increased abundance of faecal *Fusobacterium nucleatum* and a decline in *F. prausnitzii* abundance was a valuable marker for distinguishing patients with CD from healthy individuals (area under the curve of 0.841 versus 0.811) or patients with IBS (area under the curve of 0.767 versus 0.658)[142]. In another prospective multicentre study, a β-diversity analysis showed a clear separation of patients with IBD from healthy individuals and identified Gammaproteobacteria, Enterococcus and Enterococcaceae as potential biomarkers for IBD diagnosis[83].

Although several studies have reported novel emerging serum and faecal biomarkers involving molecular, epigenetic, microbial and metabolic pathways associated with gut barrier disruption and implicated in CD development and progression, these biomarkers are not recommended as a first assessment for the diagnosis of the disease[143,144].

Colorectal dysplasia surveillance

To date, colonoscopy is the gold standard for colorectal carcinoma surveillance and chromoendoscopy is recommended in the European Crohn's and Colitis Organisation guidelines[123]. Improved endoscopic imaging technology, adherence to surveillance guidelines and endoscopic management of focal dysplasia are key aspects to improve early detection of colitis-associated cancer in patients with IBD (see FIG. 3 for a proposed algorithm for surveillance for colitis-associated dysplasia or cancer in patients with CD).

Other techniques, such as narrow-band imaging, confocal laser endomicroscopy and full-spectrum endoscopy, may be potentially useful tools to improve detection of colitis-associated dysplasia, but are not currently widely used in clinical practice[119,145]. Genetic analysis of stool samples for colorectal carcinoma surveillance in patients with IBD has a detection sensitivity of 100% for carcinoma, 100% for high-grade dysplasia and 67% for low-grade dysplasia (specificity of 89% in all cases)[146].

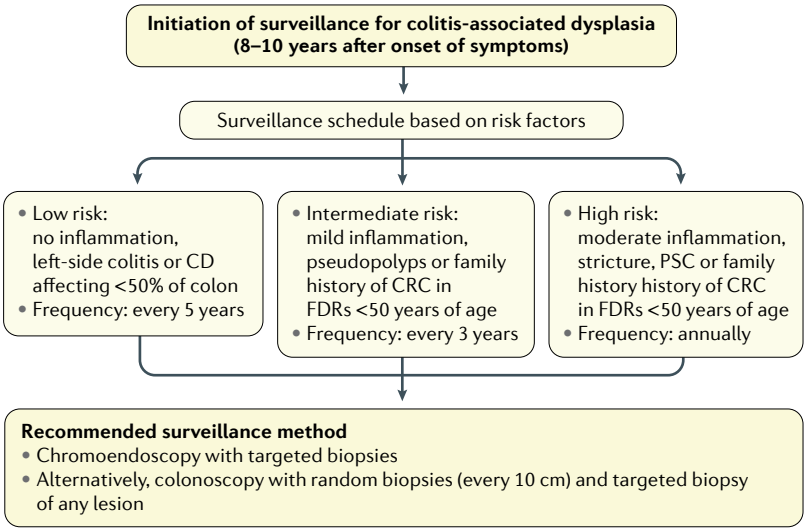

Fig. 3 | **Proposed recommendations for surveillance for colitis-associated dysplasia in patients with CD.** Surveillance should begin 8–10 years after a confirmed diagnosis of Crohn's disease (CD) at intervals that are determined by risk factors, such as primary sclerosing cholangitis (PSC), pan-ulcerative colitis (pancolitis), active inflammation, pseudopolyps or a family history of colorectal carcinoma (CRC). Patients at low risk (without active inflammation or with restricted colitis) should be endoscopically assessed (with histopathological analysis of biopsy samples) every 5 years, whereas those at intermediate risk (with 3 years of mild inflammation and/or pseudopolyps and/or a family history of CRC in first-degree relatives (FDRs) older than 50 years) should be assessed every 3 years. High-risk patients (those with 1 year of moderate inflammation, stricture, PSC or a family history of CRC in FDRs younger than 50 years) should be assessed annually.

Differential diagnosis

Differential diagnosis of other conditions, such as UC or intestinal infectious diseases, remains a challenge in some patients, owing to overlapping endoscopic, radiographic and histological features. Segmental disease distribution, transmural inflammation and non-caseating epithelioid granulomas are 'hallmarks' of CD, but sometimes they are not enough for a definitive diagnosis[2]. In 10% of patients with CD, the initial diagnosis is of unclassified colitis[147].

Another big challenge, especially in the developing world, is distinguishing CD from other intestinal diseases, such as Behçet's disease, intestinal lymphoma and intestinal tuberculosis[148,149]. Behçet's disease might present with intestinal inflammation characterized mostly by solitary ulcers and EIMs, although these EIMs differ from those in CD[150]. However, recurrent oral and genital ulcerations increase suspicion of Behçet's disease, and a positive pathergy test result supports a diagnosis of Behçet's disease[151]. Uveitis and skin involvement are frequent in Behçet's disease, as with other vasculitic lesions[151].

The clinical features of intestinal lymphoma lack specificity, and diagnosis relies on histological confirmation. Patients with intestinal tuberculosis present with fever and night sweats, ulcers of the transverse colon, patulous (distended) ileocaecal valve and unique histological features, such as caseating and/or confluent and/or large granulomas[152]. These features, together with a positive smear test result for acid-fast bacillus and detection of necrotic lymph node by cross-sectional imaging, are the only features that are specific for intestinal tuberculosis.

In addition to infectious disease, ischaemic colitis should also be considered as a differential diagnosis for CD, and often presents with mucosal oedema and erythema, with the rectum remaining intact[2].

Paediatric IBD

First-line investigation in paediatric CD relies on colonoscopy with evaluation of the terminal ileum and histological confirmation, upper GI tract endoscopy and small-bowel assessment[153]. Serology may have a role in prognosis[153]. Paediatric patients with CD who are positive for ASCA IgA or IgG have a high prevalence of terminal ileal or ileocaecal disease and are more likely to need surgery, whereas those who are positive for pANCA are more likely to have pancolitis or left-sided disease with sparing of the terminal ileum, and ileocaecal resection is usually not required[153,154].

Management

In the past decade, treatment paradigms have changed, coinciding with the development of new drugs for CD treatment. Driving these changes is the recognition that some clinical parameters are associated with an increased risk of progressive and disabling CD. In addition, it is increasingly recognized that mucosal healing (defined as restitution of the intestinal lining and regression or disappearance of endoscopic lesions) is associated with improved short-term outcomes such as reduced risk of relapse, decreased hospitalization rates, steroid-free remission in follow-up examination and resection-free intervals[1,2]. Moreover, in patients with CD, mucosal healing decreases the risk of penetrating complications and probability of surgery compared with that in patients with severe ulcerations.

Thus, mucosal healing is becoming an important treatment goal[155–157], and most experts generally recommend that management strategies strive for complete remission, which is defined as both symptomatic and endoscopic remission[157]. Moreover, mucosal healing will be complemented soon by transmural healing assessed by cross-sectional imaging techniques and histology. However, most randomized controlled trials assess either symptomatic remission or symptomatic response as outcomes, and endoscopic outcomes have been included only in contemporary clinical trials, mostly in the past decade. In addition, early initiation of highly effective therapies soon after diagnosis can lead to increased rates of clinical remission and to mucosal healing[158]. When a therapy is being started, it is important to consider the patient's perspective in regard to adherence with treatment and to QOL[159,160]. Therefore, the cornerstones of management at present are stratifying patients according to prognostic factors, striving for early disease control by treating to target and using close monitoring strategies to maintain complete remission.

Prognosis

At the time of diagnosis or of a flare, assessing the prognosis in individual patients is extremely important, as it determines the initial therapeutic approach. Several

studies have examined prognostic factors (summarized elsewhere[160,161]); in general, it is important to consider those factors that are associated with high risk of relapse, increased risk of surgery or the development of complications. Younger age at diagnosis, smoking, longer disease duration, early need for corticosteroids, fistulizing perianal CD[161,162], low serum haemoglobin and albumin levels, high serum CRP levels and high faecal calprotectin levels[163–166], the endoscopic presence of deep ulcers[167], and overall disease burden and location have been associated with increased risk of relapse or a more aggressive or complicated disease course (BOX 1). Patients lacking these factors are generally classified as low risk. High-risk patients should be considered for a top-down treatment strategy, which involves early introduction of biologic therapy, whereas a step-up treatment strategy (involving conventional therapy comprising corticosteroids and immunosuppressants) may be considered for low-risk patients (FIG. 3).

Early disease control and diagnosis

Diagnostic delay is common in CD owing to variable phenotypes and non-specific clinical findings. For example, in Europe, the median diagnostic delay for CD ranges from 5 months in France[168] to 8 months in Italy[169] and 9 months in Switzerland[170], although in other European countries it can exceed 2 years[171]. Early CD has been defined as disease that is diagnosed within 18 months of onset of symptoms, with no complications and no previous treatment with thiopurines, methotrexate and/or biologic agents. A clear definition of early CD is important to study and define the impact of early intervention on different long-term outcomes[158]. Several studies have shown that treatment of patients with CD should be started promptly (that is, when they have early CD) when the disease phenotype is inflammatory to prevent or reduce disease progression[172].

A simple, easy-to-use scoring system, the 'red flags index for suspected Crohn's disease', was developed by the International Organization for the Study of Inflammatory Bowel Diseases using early symptoms and signs of CD, including persistent perianal lesions, family history of CD, weight loss, chronic and postprandial abdominal pain, nocturnal diarrhoea, fever and absence of rectal urgency[107]. This scoring system showed a high predictive value in diagnosing CD[148]. Early diagnosis of CD (that is, soon after symptom onset) combined with early disease control during the 'therapeutic window of opportunity' (before patients develop complications, such as stenosis or penetrating disease) may be the best way to change the course of the disease, healing the mucosa and thereby decreasing hospitalizations, surgical operations, bowel damage and disability[173,174].

Treating to target and close monitoring

The therapeutic goals and end points in the management of CD continue to evolve[4]. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) programme identified two CD therapeutic targets — clinical and patient-reported outcome remission, which is defined as resolution of abdominal pain and diarrhoea or altered bowel habit, and endoscopic remission, which is defined as endoscopic disappearance of ulcers, or resolution of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy. Biomarker remission (normal CRP and faecal calprotectin levels) was considered an adjunctive target[156].

Several lines of evidence suggest that mucosal healing is the preferred treatment target. Population-based studies and meta-analyses demonstrated that mucosal healing results in improved outcomes, including decreased risk of requiring surgery, lower relapse rates and improved QOL[3,175]. In the CALM study, tight monitoring with biomarkers, including serum CRP and faecal calprotectin, to guide treatment optimization led to higher rates of mucosal healing in patients with early CD who were starting treatment with corticosteroids than in patients receiving conventional therapy[176]. This tight monitoring strategy is also associated with decreased incidence of flares, decreased hospitalization and improved QOL[176]. This tight control strategy, using currently available biomarkers, is pivotal to treatment success[176]. With the adoption of this strategy, the concept of step-up versus top-down treatment may slowly be replaced as patients requiring biologic therapy are identified earlier in the disease course or when there is a flare. However, mucosal healing as a target of the treat-to-target approach and adjustment therapy based on serial endoscopic evaluation does require more investigation. Indeed, it is unclear whether therapy should be escalated in patients who have residual activity on endoscopy but are in clinical remission. Of note, the SONIC trial showed that symptom assessment using the CDAI is not a reliable measure of the underlying inflammation, as 50% of patients in clinical remission have endoscopic and/or CRP evidence of residual, active CD, whereas other patients with symptoms have normal endoscopic findings and CRP levels[177]. Therefore, a CDAI below the cut-off might mask endoscopic activity.

Box 1 | **Prognostic factors for aggressive course of Crohn's disease**

Patient features

Young age at diagnosis (<40 years)[161,162]
Polymorphisms in *NOD2*, *ATG16L1* and *MDR1* (also known as *ABCB1*)[35–37]
Smoking[2,20–23]

Disease features

Overall disease burden and location and long duration of disease[161]
Perianal disease[161,162]
Stricturing disease[161]
Upper gastrointestinal tract Crohn's disease (oesophagus, stomach, duodenum and jejunum)[162]
Need for corticosteroids on the first flare-up[162]
Lack of mucosal healing after induction of clinical remission[162]
Endoscopic appearance (for example, the presence of deep ulcers)[167]
Epithelioid granulomas detected by histological analysis of biopsy specimen[2]

Laboratory markers

High serum levels of C-reactive protein, anti-*Saccharomyces cerevisiae* antibodies, anti-outer membrane porin C antibodies and anti-CBir1 antibodies[126,163]
High faecal calprotectin levels[163–166]
Low serum levels of albumin and haemoglobin[163–166]

Drug withdrawal

Although there is an emerging consensus about the importance of initiating treatment soon after diagnosis and a treat-to-target strategy in the management of IBD, debate continues about the risks, benefits and timing of stopping treatment when patients are in stable remission. Moreover, when deciding whether to discontinue treatment, clinicians should consider the high cost of indefinite maintenance therapy and cumulative treatment-related toxicity, which increases with the treatment duration. Relapse rates increase after immunosuppressant monotherapy is stopped following a period of remission (30% in CD), whereas there is no increase in relapse rates in patients who discontinue immunosuppressant therapy after combination therapy[178]. In the STORI study, the relapse rate was ~52% at 2 years after withdrawal of an anti-TNF drug in patients receiving combination therapy, indicating that a subset of patients in deep remission have a very low risk of relapse[179].

Conventional non-biologic therapies

Induction therapy. Corticosteroids, such as budesonide and prednisone, have been the cornerstone of CD management for many decades. These agents are recommended for the treatment of mild-to-moderate ileal and moderate-to-severe ileocolonic CD. Steroids have a rapid onset of action and are indicated to induce remission in CD but are not indicated for maintenance of disease remission. The third European evidence-based consensus on the diagnosis and management of Crohn's disease from 2016 recommends daily oral administration of budesonide (9 mg) for mild, active, localized ileocaecal CD[97]. The usual starting dose for induction of remission in active CD is 40–60 mg prednisone or equivalent. A higher starting prednisone dose (1 mg/kg) seems to increase the remission rate in the short term[180,181] (weeks to months) but no comparative studies have been performed. Systemic steroids are the first-line therapy for colonic CD[97]. In mild-to-moderate cases of CD where steroids are a contraindication, the British Society of Gastroenterology recommends exclusive enteral nutrition (the use of a completely liquid diet) to induce remission[182].

Mesalazine was approved by the FDA in 1987 for the treatment of CD. However, there is a lack of evidence for the efficacy of mesalazine in either induction or maintenance therapy in CD. Antibiotics are indicated in the case of perianal complications such as abscesses, whereas there is a lack of evidence for the efficacy of antibiotics in reducing inflammation in CD.

Maintenance therapy. Immunosuppressants and biologic agents have shown efficacy in maintenance therapy in CD. The use of thiopurines is limited to the maintenance of CD remission[97,182]. For example, In the AZTEC study, the early use of azathioprine was no more effective than placebo in achieving sustained corticosteroid-free remission but a post hoc analysis revealed that azathioprine was more effective than placebo in preventing moderate-to-severe relapse[183,184]. Similarly, in the RAPID trial, administration of azathioprine within 6 months of a CD diagnosis was no more effective than conventional management, such as with corticosteroids, in increasing the duration of clinical remission[185]. However, azathioprine has a role in maintaining remission in patients with CD who received corticosteroid induction therapy[185,186]. Moreover, although the primary outcomes were not achieved in the AZTEC and RAPID trials, real-life data support the use of thiopurines in reducing the risk of intestinal resection[187]. Currently, the antimetabolite methotrexate is increasingly being used in combination with anti-TNF agents to prevent immunogenicity towards these biologic therapies, although its efficacy in combination therapy requires additional investigation[188].

In general, biologic therapies, such as anti-TNF agents, ustekinumab and vedolizumab, are favoured over thiopurines in clinical practice, especially in high-risk patients. For example, in the SONIC study, disease remission rates were higher with anti-TNF therapy than with azathioprine[189]. If thiopurine monotherapy is the preferred option due to economic and reimbursement issues, its use should be restricted to selected low-risk patients[189].

Biologic therapies

Biologic agents can be used for induction and/or maintenance therapy in the management of CD. The development of biologic therapies is an important step in the treatment of IBD, as these drugs induce remission and result in response rates that are not achieved with other therapies. Anti-TNF therapies (such as infliximab, adalimumab and certolizumab) have revolutionized the treatment of CD in the past two decades. With the introduction of infliximab and adalimumab biosimilars, these agents have become increasingly available in many places in the world. Newer biologic agents, such as ustekinumab and vedolizumab, are also effective and are approved in the USA and Europe for treating moderate-to-severe CD[77,190]. The absence of head-to-head studies, or companion diagnostic testing to predict response or non-response, results in major knowledge gaps in the treatment of CD. Physicians often make their decisions on the basis of personal experience with a particular class of drug while considering efficacy, safety and patient comorbidities. Patients often choose therapies on the basis of safety concerns and the most common routes of administration, mostly preferring oral or subcutaneous administration rather than intravenous administration[191]. Anti-TNF agents are first-line therapy in high-risk patients[97], because of decades of clinical experience, including clinical experience of efficacy and of low incidence of adverse events, as well as a lack of robust data on the efficacy of vedolizumab and ustekinumab in inducing mucosal healing. Anti-TNF therapies and ustekinumab are favoured over vedolizumab, which seems to be slightly slower acting, when rapid onset of action is preferred[97]. However, vedolizumab is the agent of choice in patients with multiple comorbidities or safety concerns, such as elderly patients, mostly in relation to infection risk because of its intestinal selectivity[190]. Of interest, the VARSITY trial compared the effectiveness of vedolizumab and adalimumab in

patients with moderate-to-severe UC; vedolizumab seemed to be superior to adalimumab in achieving clinical remission and endoscopic improvement but not corticosteroid-free clinical remission[192]. Future trials might show the same results in CD. Anti-TNF agents are preferred in patients with severe EIMs, such as uveitis, ankylosing spondylitis or pyoderma gangrenosum. Optimization strategies with biologic agents, such as dose escalation or frequency, are also an important consideration to increase efficacy. Whether immunosuppressive therapy with methotrexate or a thiopurine should be included in induction treatment with a biologic agent is still debated. A drawback of currently available biologic agents is their immunogenicity; however, the immunogenicity of vedolizumab and ustekinumab seems to be lower than that of anti-TNF drugs[169]. Studies testing the efficacy of combination therapy with these biologic agents and an immunosuppressant compared with biologic monotherapy are lacking.

Therapeutic drug monitoring (TDM) is crucial when a patient stops responding to anti-TNF therapy, as there is an association between drug concentrations in the blood and clinical outcomes[193–196]. Proactive TDM has been evaluated, and negative results have been reported in multiple studies, although these studies had limitations (such as heterogeneous patient populations, rigid therapeutic drug level ranges and the lack of using both a TDM approach and a biomarker approach)[195]. Further studies are needed to clarify the utility of TDM in this context. Furthermore, there is limited evidence for the utility of TDM in therapy with vedolizumab or ustekinumab[196].

There are few or no data on treatment approaches in patients who fail to respond or stop responding to biologic agents. Switching between different non-anti-TNF biologic drugs or switching to another anti-TNF biologic drug is an option. In patients who fail to respond to drugs of one mechanism of action, even if the dose is optimized, it seems logical to switch to drugs that have a different mechanism of action[197–199]. As reported above, reactive TDM is more efficacious than empirical dose escalation because it is more cost-effective, but proactive TDM is useful to optimize care in patients with IBD[195].

Most of the IBD therapies that are commonly used in Western countries, including steroids, antibiotics, thiopurines and anti-TNF agents, are also used in Asian countries[200] (although medical practice differs among Asian countries). In general, anti-TNF agents are less frequently used in Asia than in Western countries owing to cost, lack of health insurance reimbursement, concern about opportunistic infections and a lack of clinician experience with these drugs[200,201]. For example, in a cross-sectional study comparing the management of patients with CD in different Asian regions, 40% of patients in Melbourne, Australia, received an anti-TNF agent compared with only 11% of patients in Hong Kong[201]. Approaches that are untested or lack evidence of efficacy, such as alternative and complementary medicine, ayurvedic medicine and homeopathy, are common medical practice for IBD in South Asia and Southeast Asia[200].

T_H17 cells and their pathways may have a predominant role in the development of chronic inflammation in IBD. Immature T_H17 cells differentiate into mature, polarized T_H17 cells in response to proinflammatory cytokines, such as IL-12, IL-23, IL-27 and IL-35. Blockade of both IL-12 and IL-23 is effective in treating the chronic intestinal inflammation in both CD and UC. Indeed, T_H17-activating proinflammatory cytokines are produced in excess in IBD[202], and polymorphisms in several T_H17-related genes are associated with IBD[202]. However, in animal models of experimental colitis, IL-17A blockade results in exacerbated intestinal inflammation by affecting epithelial tight junction integrity, suggesting that IL-17A has a tissue-protective role. Conversely, intestinal inflammation is clearly reduced in *Il17a*-knockout mice. The utility of IL-17A inhibition for treating patients with CD is also controversial, as the human anti-IL-17A antibody secukinumab showed no benefit in patients with CD[203].

Pregnancy

In pregnant women, gut microbial diversity is reduced compared with that in healthy women, although only at the beginning of pregnancy, and returns to normal in middle and late pregnancy, suggesting that pregnancy is safe and beneficial for patients with IBD[204].

Overall, pregnancy has been reported to have a beneficial effect in CD, as it seems to activate tolerance and suppressive modulation with an increased T_H2 or tolerogenic phenotype. Furthermore, changes in the levels of pregnancy hormones seem to positively affect the epithelial barrier. For example, the levels of human chorionic gonadotropin, oestrogen and progesterone increase rapidly during pregnancy and have anti-inflammatory effects in animal models of colitis, including reduced IL-17 levels and increased IL-10 levels[204,205]. Of note, gut microbiota changes during pregnancy have not been shown to have a beneficial effect in CD. Several factors might affect whether pregnancy will be 'protective', such as ongoing disease activity before conception, gut microbiota- and hormone- or diet-induced changes, and underlying genetic risk factors[205].

Quality of life

HRQOL is a multidimensional concept that includes physical, emotional and social features of health perception and health functioning. The chronic and progressive nature of CD has a debilitating effect on a patient's social, educational, professional and familial activities (FIG. 4). The main stressors include abdominal discomfort, bloody stools, diarrhoea, faecal urgency, impaired appetite and weight loss, a need for long-term use of immunosuppressant or immunomodulatory medication, and hospitalization or surgery. Increased perceived stress, decreased social support, higher number of relapses and, possibly, female sex may be associated with worse HRQOL in patients with IBD[13].

Addressing HRQOL in patients with an aggressive and destructive disease such as CD should be included in routine clinical practice because it informs clinicians about patients' perception of their health and the effect of treatments. Measuring QOL involves assessing domains such as sexual activity, social activity, ability to work or attend school and participate in

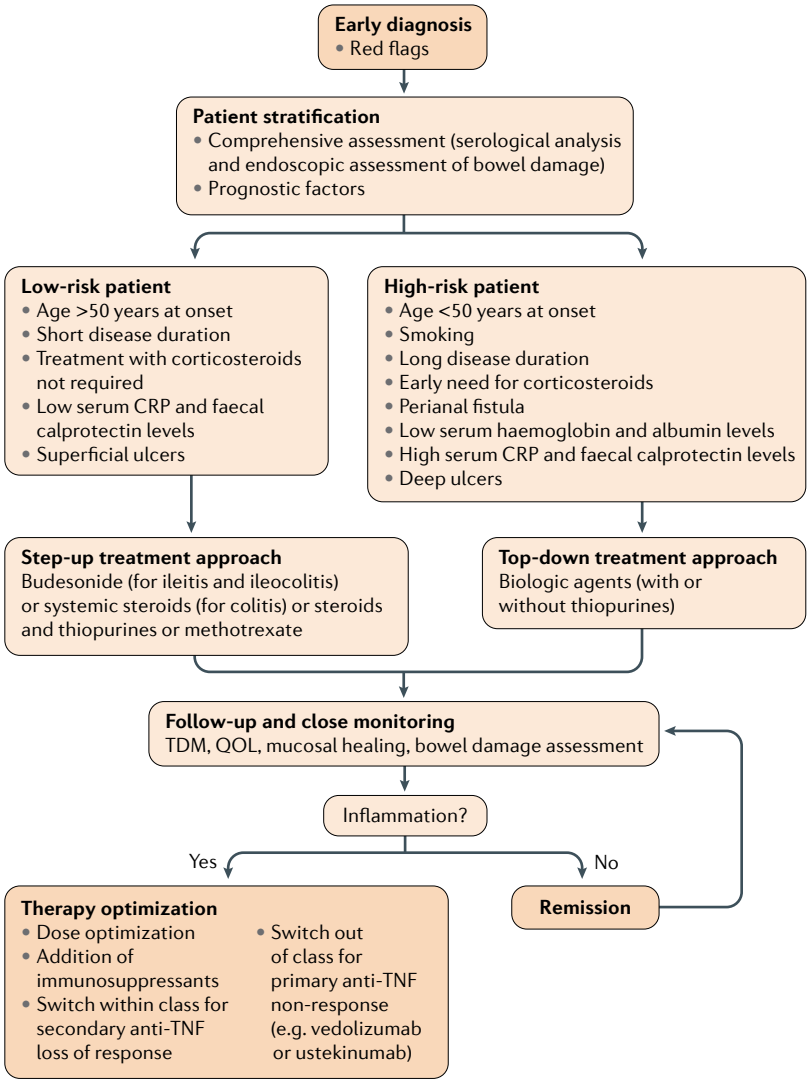

Fig. 4 | **Treatment approaches in Crohn's disease.** The treatment approach in Crohn's disease should be based on patient stratification at diagnosis into those at low risk and those at high risk of disease progression. Early diagnosis (that is, soon after symptom onset) may be facilitated by the use of the red flags system (symptoms or signs suggestive of Crohn's disease). Stratification is achieved by extensive assessment of disease activity (by serological and faecal analysis and endoscopic assessment of bowel damage) and prognostic factors, such as disease duration, age, smoking, early need for corticosteroids, complications, and ulcers. Patients at low risk of disease progression are treated by a step-up approach, involving induction therapy with corticosteroids, either intestinally targeted (using budesonide) or systemic (prednisone), or steroids in combination with thiopurines or methotrexate. Patients at high risk of disease progression are treated by a top-down approach, involving induction therapy comprising biologic agents (such as anti-tumour necrosis factor (anti-TNF) therapies, the anti-integrin antibody vedolizumab and the anti-cytokine antibody ustekinumab), with or without thiopurines. Close monitoring is useful during follow-up to measure mucosal healing and assess quality of life (QOL), and involves therapeutic drug monitoring (TDM), serum and faecal tests and endoscopic evaluation of bowel damage. If no inflammation is detected at follow-up (that is, remission), disease activity is closely monitored in patients. However, if inflammation is detected, then a number of steps are undertaken to identify alternative treatments, such as those with a different mechanism of action or in a different therapeutic class. CRP, C-reactive protein.

sports and recreation, and body image[206]. In addition, HRQOL can be measured using either general instruments that are applicable to various chronic diseases or disease-specific instruments. In the past 10 years, many studies have focused on the development of instruments to measure HRQOL for better evaluation of patient health and therefore better quality of care. In a review of HRQOL measurements and IBD, the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ-32) was the most widely used and had the strongest evidence of being reliable, valid and responsive for adult patients with IBD[207].

The 10-item short IBDQ (SIBDQ) and 9-item IBDQ (IBDQ-9) are shorter versions of IBDQ-32 that are simpler and less time-consuming to complete and have been translated into different languages, facilitating their use worldwide[208]. In several studies, HRQOL was lower in patients with CD than in healthy individuals and disease activity correlated with poor HRQOL[209]. In addition, the presence of EIMs and an increased number of relapses per year are associated with substantially lower HRQOL scores on the IBDQ-32 scale[210]. Female sex, tobacco use and corticosteroid therapy were related to poor HRQOL in a longitudinal, prospective study of 231 patients with CD, which also found that HRQOL was underestimated by physicians who were treating patients with CD[211]. Furthermore, CD has a substantially negative effect on family life and professional performance[212].

Treatment is an additional important stressor that affects HRQOL in patients with CD. In a study of 169 patients with CD, HRQOL was lower in patients treated with corticosteroids or azathioprine than in patients receiving no treatment[213]. Furthermore, surgery and the potential need for an ostomy are additional stressors for patients with CD. Of note, there was no substantial difference in HRQOL in patients achieving remission after surgery compared with patients in remission without surgery[214]. Fatigue in chronic diseases such as CD has been increasingly recognized as impairing QOL, even in patients with IBD who are in remission[215]. In both CD and UC, fatigue has been shown to affect HRQOL independently of disease activity or anaemia[215].

Most patients with CD are affected by the disease in the most productive years of their lives — during their working or reproductive years. The symptom that patients with CD refer to as the most difficult is pain. Indeed, in 90% of patients, mainly abdominal pain is significantly associated with diminished QOL[216]. Disease activity is another stressor associated with decreased QOL[211]. Social support is generally understood to have a positive influence on outcomes such as QOL. The QOL of patients with IBD is positively influenced by spousal support[210]. Therapeutic strategies have been modified to reduce the important stressors and thereby improve QOL, for example by inducing and maintaining remission and avoiding complications[182]. In clinical practice, measuring HRQOL can have a direct impact on the improvement of patient outcomes[217] (FIG. 5).

Outlook

CD is a chronic, systemic, progressive and destructive inflammatory disorder that is increasing in incidence worldwide. In the past two decades, the concept of progressive disease has emerged with a definition of CD as a destructive disease involving accumulating damage that leads to disabling complications, such as strictures,

abscesses and fistulas. In the past few years, therapeutic strategies have been directed towards achieving mucosal healing, which has resulted in disease severity and bowel damage being redefined[218,219]. Various patient characteristics and disease features assessed at diagnosis have recently been reported as prognostic factors (BOX 1) for an aggressive disease course in patients with CD[219].

Disease progression

Approximately 50% of patients with CD show disease progression in the 10 years after diagnosis. Consequently, new tools have been developed to assess bowel damage, defined as cumulative structural damage to the digestive system, and to stratify patients and prevent complications, such as hospitalization and surgery. The Lémann score is the first tool that measures the cumulative structural damage to the bowel in CD, by endoscopic assessment of the presence of strictures and penetrating lesions (that is, fistulas and abscesses), and the requirement for surgical resection. The score facilitates the identification of patients who are at high risk of rapid disease progression, thereby informing decisions to modify therapy[220]. Bowel damage and the Lémann score have been demonstrated to be independent prognostic factors for the requirement of intestinal surgery and CD-related hospitalization during patient follow-up[4,103].

The International Organization for the Study of Inflammatory Bowel Diseases selected the most important attributes of IBD to create an index to define overall disease severity. For CD, the presence of mucosal lesions (15.8%), a history of a fistula (10.9%), a history of an abscess (9.7%) and a history of intestinal resection (74%) explained the overall disease severity[221].

Preventing disease progression is an achievement that is sorely needed in the management of CD. Thus, the focus of future research should be to identify predictive biomarkers, and the introduction of toolkits to define and measure disease severity and progression, such as the Lémann score or CD severity indices, in clinical practice and clinical trials might allow early treatment that could change the natural history of CD.

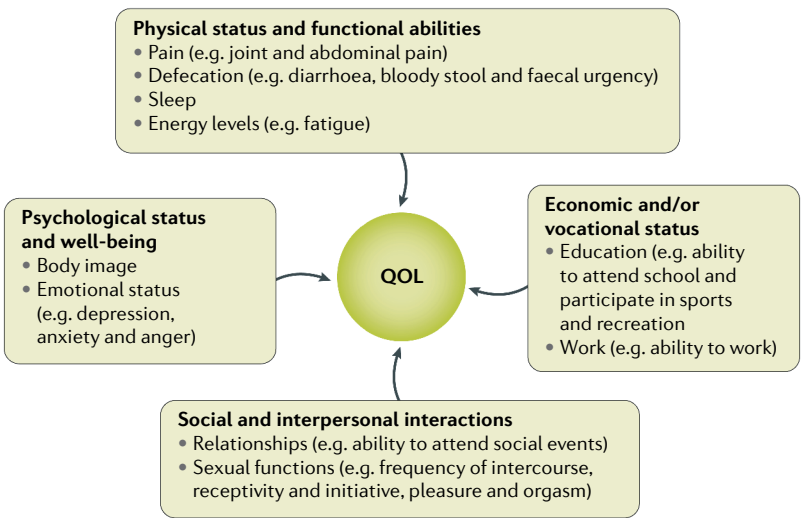

Fig. 5 | **Factors that affect QOL domains in Crohn's disease.** The quality of life (QOL) of patients is assessed in physical, psychological, social and economic domains. Quality of life in patients with Crohn's disease is affected by disease symptoms, complications and extraintestinal manifestations as well as the therapies that are used to treat the disease.

Pathogenesis

Studies of dysfunction in other organs might represent a reservoir for knowledge transfer to illuminate pathogenetic mechanisms in the intestines. For example, more than one third of patients with CD develop a distinct fibrostenosing phenotype, which is characterized by progressive narrowing of the intestinal lumen that can lead to bowel obstruction[222,223], and there is currently no approved or effective treatment for intestinal fibrosis in IBD. Studies in the liver introduced the new concept of reversibility of fibrosis, the extent of which is dependent on the stage of fibrosis. Soon, new antifibrotic drugs developed from these studies of liver fibrosis will be combined with biologic therapies, and early stratification of individual patients with CD who are at risk of a stricturing disease course should provide the ideal patient population for these treatments.

Treatment

Personalized medicine is emerging in the treatment of CD, and represents a shift from controlling the symptoms of the disease to preventing disability in the long term[224]. Personalized medicine has been defined as customized health care informed by an individual's unique genomic, clinical and environmental information[225]. In CD, stratifying patients on the basis of severity indices represents the future approach in the era of personalize medicine[160]. Models to predict disease outcomes are in development, such as a validated Web-based predictive tool that requires the inclusion of clinical, serological, genetic, endoscopic and imaging information[226]. Soon, personalized medicine will involve incorporating not only symptoms, serological markers and endoscopic and histological assessment into our patient evaluations but also genetic and molecular phenotypes, added to our existing knowledge of clinical and demographic factors.

Current available treatments for CD have limitations, and new options are needed. Although targeted biologic therapies have been a significant advance, parenteral administration and the potential for immunogenicity are major drawbacks of these therapies. A host of orally administered small molecules are emerging as potential therapies in CD, including selective Janus kinase (JAK) inhibitors (for example, filgotinib and upadacitinib)[197] and sphingosine-1-phosphate receptor 1 (S1PR1) agonists (for example, ozanimod and etrasimod)[198]. In addition, selective IL-23 inhibition (for example, the anti-p19 antibodies risankizumab and brazikumab) has shown promise[199]. Although the antibiotic regimens that have been studied to date have not consistently demonstrated efficacy, non-absorbable antibiotics, such as rifaximin, warrant further study in CD. In addition, manipulating the microbiota through the diet or other means, including faecal microbiota transplantation, may prove to be beneficial and is also being investigated.

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Author contributions
Introduction (G.R., L.P.-B. and S.D.); Epidemiology (S.C.N.); Mechanisms/pathophysiology (A.K.); Diagnosis, screening and prevention (P.G.K. and M.A.); Management (R.P.); Quality of life (G.R., A.S., L.P.-B. and S.D.); Outlook (G.R., A.S., L.P.-B. and S.D.).

Competing interests
S.D. has served as a speaker, consultant and advisory board member for Schering-Plough, AbbVie, Merck Sharp & Dohme, UCB Pharma, Ferring, Cellerix, Takeda Pharmaceutical Company, Nycomed, Pharmacosmos, Actelion, Alpha Wasserman, Genentech, Grünenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, Johnson & Johnson and Nikkiso Europe GmbH. L.P.-B. has received consulting fees from AbbVie, Amgen, Biogaran, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Ferring, Genentech, HAC Pharma, Hospira, Index Pharmaceuticals, Janssen, Lilly, Merck, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilege, Sandoz, Takeda, Therakos, Tillotts, UCB Pharma and Vifor and lecture fees from AbbVie, Ferring, HAC Pharma, Janssen, Merck, Mitsubishi, Norgine, Takeda, Therakos, Tillotts and Vifor. A.S. has acted as a consultant or speaker for Ethicon, Olympus, Frankenman, Transenterix (not active), Tigenyx, Pfizer, Takeda and Sandoz. P.G.K has been a lecturer for AbbVie, Janssen, Pfizer and Takeda and is a member of the advisory board of AbbVie, Pfizer and Takeda. A.K. has served as an adviser to Boehringer Ingelheim, Ferring, Genentech, GlaxoSmithKline, Gilead, Hospira, Janssen, Pfizer, and VHSquared. R.P. has received consultant and/or lecture fees from AbbVie, Amgen, AstraZeneca, Axcan Pharma (now Aptalis), Biogen Idec, Bristol-Myers Squibb, Centocor, ChemoCentryx, Eisai Medical Research Inc., Elan Pharmaceuticals, Ferring, Genentech, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Millennium Pharmaceuticals (now Takeda Oncology), Ocera Therapeutics Inc., Otsuka America Pharmaceutical, Pfizer, Shire Pharmaceuticals, Prometheus Laboratories, Schering-Plough Corporation, Synta Pharmaceuticals Corp., Teva, UCB Pharma and Warner Chilcott. S.C.N. has received consulting and speaker fees from AbbVie, Ferring, Janssen, Menarini and Takeda, has served as a scientific advisory board member for AbbVie, Ferring and Takeda and has received research grants from AbbVie, Ferring and Janssen. The other authors declare no competing interests.

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