Check for updates

Personalize, participate, predict, and prevent: 4Ps in inflammatory bowel disease

Marco Vincenzo Lenti[1,2], Maria Lia Scribano[3], Livia Biancone[4], Rachele Ciccocioppo[5], Daniela Pugliese[6], Luca Pastorelli[7,8], Gionata Fiorino[9,10], Edoardo Savarino[11], Flavio Andrea Caprioli[12], Sandro Ardizzone[13], Massimo Claudio Fantini[14,15], Gian Eugenio Tontini[16], Ambrogio Orlando[17], Gianluca Matteo Sampietro[18], Giacomo Carlo Sturniolo[11], Giovanni Monteleone[4], Maurizio Vecchi[12], Anna Kohn[19], Marco Daperno[20], Renata D'Incà[11], Gino Roberto Corazza[1,2] and Antonio Di Sabatino[1,2]*

[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy, [2]Department of Internal Medicine, San Matteo Hospital Foundation, Pavia, Italy, [3]Villa Stuart, Multi-Speciality Clinic, Rome, Italy, [4]Unit of Gastroenterology, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy, [5]Gastroenterology Unit, Department of Medicine, A.O.U.I. Policlinico G.B. Rossi and University of Verona, Verona, Italy, [6]CEMAD Digestive Disease Center, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, [7]Liver and Gastroenterology Unit, ASST Santi Paolo e Carlo, Milan, Italy, [8]Department of Health Sciences, University of Milan, Milan, Italy, [9]IBD Unit, Ospedale San Camillo-Forlanini, Rome, Italy, [10]Department of Gastroenterology, San Raffaele Hospital and Vita-Salute San Raffaele University, Milan, Italy, [11]Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy, [12]Gastroenterology and Endoscopy Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda, Ospedale Maggiore Policlinico and Università degli Studi di Milano, Milan, Italy, [13]Gastroenterology and Digestive Endoscopy Unit, ASST Fatebenefratelli Sacco, Milan, Italy, [14]Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy, [15]Gastroenterology Unit, Azienda Ospedaliero-Universitaria (AOU) di Cagliari, Cagliari, Italy, [16]Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, Italy, [17]Inflammatory Bowel Disease Unit, Azienda Ospedaliera Ospedali Riuniti "Villa Sofia-Cervello" Palermo, Palermo, Italy, [18]Division of General and HBP Surgery, Rho Memorial Hospital, ASST Rhodense, Rho, Milano, Italy, [19]Gastroenterology Operative Unit, Azienda Ospedaliera San Camillo-Forlanini FR, Rome, Italy, [20]Division of Gastroenterology, Ospedale Ordine Mauriziano di Torino, Turin, Italy

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a complex, immune-mediated, disorder which leads to several gastrointestinal and systemic manifestations determining a poor quality of life, disability, and other negative health outcomes. Our knowledge of this condition has greatly improved over the last few decades, and a comprehensive management should take into account both biological (i.e., disease-related, patient-related) and non-biological (i.e., socioeconomic, cultural, environmental, behavioral) factors which contribute to the disease phenotype. From this point of view, the so called 4P medicine framework, including personalization, prediction, prevention, and participation could be useful for tailoring *ad hoc* interventions in IBD patients. In this review, we discuss the cutting-edge issues regarding personalization in special settings (i.e., pregnancy, oncology, infectious diseases), patient participation (i.e., how to communicate, disability, tackling stigma and resilience, quality of care), disease prediction (i.e., faecal markers, response to treatments), and prevention (i.e., dysplasia through endoscopy, infections through vaccinations, and post-surgical recurrence). Finally, we provide an outlook discussing the unmet needs for implementing this conceptual framework in clinical practice.

KEYWORDS

clinical complexity, Crohn's disease, internal medicine, precision medicine, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is an immune-mediated, lifelong, chronic, and disabling condition (1–4), which is constantly increasing worldwide (5), affecting individuals of any age and gender. IBD includes two main entities, namely ulcerative colitis (UC) and Crohn's disease (CD), both causing intestinal (e.g., abdominal pain, diarrhoea and/or constipation, rectal bleeding, perianal symptoms) and extraintestinal (e.g., fatigue, anaemia, micronutrient deficiencies, arthritis, fertility issues) manifestations, deeply affecting patients' quality of life, and social and sexual relationships (1, 2, 4). Over the last three decades, our knowledge about this condition has greatly improved, and the treatment paradigm has shifted from the use of unselective anti-inflammatory and immunosuppressive agents (e.g., mesalamine, corticosteroids, methotrexate, azathioprine, 6-mercaptopurine) to the use of more selective, pathogenesis-oriented, therapies (e.g., biological agents, small molecules) (6). Given all the proteiform and multifaceted aspects that should be taken into account, namely patient-, disease-, and drug-related factors (Figure 1), IBD can be considered as a clear example of a clinically complex disease (7), in which both biological and non-biological factors play a role in determining patients' outcomes.

For these reasons, IBD should be considered as a systemic disorder, rather than as a specialty-oriented condition. In fact, although authoritative guidelines are available (8–11), they do not comprehensively consider all the possible aspects that may influence decision-making and patients' outcomes, such as specific age groups (e.g., childhood, age of transition, elderly), specific situations (e.g., pregnancy and lactation, poor medication adherence, socioeconomic deprivation), and comorbidities (e.g., cancer, autoimmunity, infectious diseases). From this point of view, the so called 4P medicine (12), which stands for predictive, preventive, personalized, and participatory, might be considered as a proper framework for tailoring interventions

for IBD at a patient—rather than at a disease—level, depending on their specific needs. Three main drivers have been implicated in the emergence of the 4P medicine, including the expansion of systems biology and systems medicine, the digital revolution, and the consumer-driver healthcare and social networks (12). All of these have indeed fuelled much interest in more precise and personalized medicine.
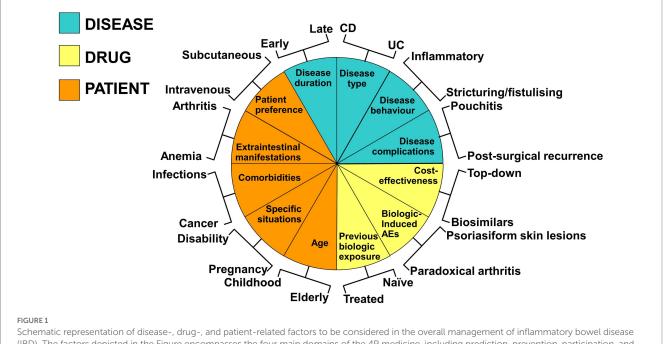
In this narrative review, within the framework of the 4P medicine, we have chosen a series of the most controversial and the currently debated issues in IBD, with an expert-based approach. Specifically, we have chosen three main topics per each "P" included in the framework. Additionally, we have also commented on the unmet needs in the field of IBD, which could soon be implemented.

No new data were generated or analyzed in support of this paper.

Personalize

Tailoring treatment of IBD in pregnant women

IBD commonly affects most patients in their reproductive age. Women with IBD experience significant concerns when considering pregnancy, especially related to the potential risks of drugs on pregnancy and foetal development, which may lead to a poor adherence to the therapy (13). It is of paramount importance to achieve a stable disease remission prior to conception and maintain a quiescent disease throughout pregnancy (14). Therefore, patients must be aware that if the treatment is discontinued, the risk of maternal and foetal complications related to disease relapse outweighs the potential adverse effects of medications. Preconception counseling is recommended, as it can improve drug adherence and pregnancy outcomes (15).

FIGURE 1
Schematic representation of disease-, drug-, and patient-related factors to be considered in the overall management of inflammatory bowel disease (IBD). The factors depicted in the Figure encompasses the four main domains of the 4P medicine, including prediction, prevention, participation, and personalization. Current guidelines do not comprehensively cover these aspects, that all pertain to an internal medicine setting. Indeed, many other variables not depicted in the Figure should also be considered and discussed with patients.

Many studies have evaluated the impact of therapy on the course and outcome of pregnancy in IBD women. However, determining the safety of drugs in this context is challenging as several factors such as disease activity, concomitant therapies, comorbidities and other maternal aspects can confound the study results. Most drugs have a favorable safety profile for use in pregnant patients (Table 1). Aminosalicylates are considered safe, therefore guidelines recommend their continuation throughout pregnancy (16, 17). In women who have an IBD flare during pregnancy, corticosteroids may be employed (16–18). The PIANO registry, including 1,490 pregnant women with IBD, showed an association between corticosteroid use and preterm birth, intrauterine growth restriction and low birthweight (19). However, the risk might be associated with IBD activity rather than drug use. Budesonide may be preferred for the treatment of mild-to-moderate CD relapse (17). The antibiotics metronidazole and ciprofloxacin should be avoided during pregnancy, especially in the first trimester (16). An increased rate of preterm birth has been observed with use of thiopurines (4–6). However, more recent data reported no heightened risk of adverse pregnancy outcomes associated

with these medications (20, 21). Therefore, therapy with thiopurines should be maintained throughout pregnancy because the benefits outweigh potential risks (17). Methotrexate is absolutely contraindicated in pregnancy, due to its teratogenic and abortifacient action (16–18). Evidence on the use of cyclosporine in IBD patients is limited to pregnant women with a severe UC refractory to treatment (22). An increased rate of prematurity and low birthweight has been observed.

Results of several studies suggest low risk for use of anti-tumor necrosis factor (TNF) agents during pregnancy (23). In the PIANO and TREAT registers no increase in congenital abnormalities or adverse pregnancy outcomes was found among women who received anti-TNFs compared to the unexposed IBD control group (21, 24). The anti-TNF drugs, aside from certolizumab pegol, cross the placenta in the second and, especially, in the third trimester. Discontinuing the therapy around gestational week 24–26 is recommended by European guidelines to reduce anti-TNF exposure of the foetus (16). Indeed, this is recommended for patients who are in stable and complete remission, otherwise this therapy can be continued. Some studies,

TABLE 1 Medical management of IBD during fertility and pregnancy.

Medication	Pregnancy safety	Recommendations
Aminosalicylates		
Mesalazine	Low risk	All mesalazine formulations are now phthalate-free. Dibutyl phthalate coating reported to be teratogenic in animals
Sulfasalazine	Low risk	Folate supplementation: 2 mg/day
Corticosteroids		
Systemic corticosteroids	Low risk	Use for IBD relapse. Possible increased risk of cleft lip/palate (first trimester exposure), not confirmed by all studies
Budesonide	Low risk, limited data	Use for ileocaecal CD relapse
Antibiotics		
Metronidazole	Avoid in the first trimester	Short-term courses in second and third trimesters for pouchitis and perianal CD. Possible increased risk of cleft lip/palate (first trimester exposure)
Ciprofloxacin	Avoid in the first trimester	Short-term courses in second and third trimesters for pouchitis and perianal CD. Potential toxicity to cartilage (first trimester exposure)
Immunomodulators		
Thiopurines	Low risk	When combined with biologic agents consider stopping in appropriate women, given a possible increased risk of infant infections
Methotrexate	Contraindicated	Must be discontinued 3–6 months before attempting conception
Cyclosporine	Unclear, limited data	Rescue therapy in refractory UC to avoid colectomy
Biologics Anti-TNF		
Infliximab	Low risk	Consider discontinuing the drug around gestational week 24–26
Adalimumab	Low risk	Consider discontinuing the drug around gestational week 24–26
Golimumab	Low risk	Consider discontinuing the drug around gestational week 24–26
Certolizumab pegol	Low risk	Continue throughout pregnancy
Anti-α4β7 integrin		
Vedolizumab	Likely low risk, limited data	Individualized decision
Anti-interleukin 12–23		
Ustekinumab	Likely low risk, limited data	Individualized decision
Janus kinase inhibitor		
Tofacitinib	Contraindicated, limited data	The manufacturer recommendation is to use contraception during treatment with the drug

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; TNF, tumor necrosis factor.

including the PIANO registry and the European TEDDY study, showed that anti-TNF use throughout pregnancy was not associated with an increased rate of infantile infections or serious infections (21, 25). Stopping anti-TNF therapy before the third trimester is an individualized decision based on both IBD activity and the woman's risk profile (18).

Available data on the use of vedolizumab in pregnancy is limited. A retrospective study of 24 pregnancies exposed to vedolizumab reported some maternal and neonatal complications (26). Different results arise from a prospective comparison study on 24 pregnancies in 21 women treated with vedolizumab, whose use appeared low risk (27). Likewise, no concerns were observed in the case–control European CONCEIVE study, or in the PREGNANCY-GETAID study (28, 29). Therefore, the use of vedolizumab during pregnancy seems to convey a low risk, however no firm conclusion can be drawn, and a personalized decision should be made.

The effects of ustekinumab in pregnant women with IBD were evaluated in 29 pregnancies in the PREGNACY-GETAID study, without negative signals on maternal or neonatal outcomes (30). This data was confirmed by the preliminary results from the DUMBO prospective registry (31). Thus, ustekinumab appears to be safe during pregnancy, however the experience is limited, and its use should be individualized.

Tofacitinib, at doses exceeding human dose, is teratogenic in animals (18). Limited reported outcomes of pregnancy and new-borns in women on tofacitinib appeared to be similar to those observed in the general population (31, 32). Nevertheless, at present, the use of tofacitinib during pregnancy is contraindicated.

Tailoring treatment of IBD in cancer patients

Cancer risk is increased in IBD patients with a history of cancer, regardless of IBD-related treatments, as in the general population. The risk of new or recurrent cancer in patients with a present or past history of cancer using immunomodulators is under investigation. Most of these studies include IBD patients with less invasive cancer types, associated with a low risk of recurrence and limited follow up, thus limiting this analysis. The frequent combined conventional immunomodulators and biologics also does not allow an appropriate assessment of the risk of new/recurrent cancer using each specific treatment in IBD. Moreover, the time interval between diagnosis or remission of cancer and immunomodulators use differ among studies. Finally, patients with less severe cancer or with a lower risk of recurrence has mostly been considered. Overall, a joint management with oncologists shared with patients and follow up tailored on a patient's basis is required when considering immunomodulators in IBD patients with a history of cancer.

Thiopurines use in IBD has been associated with a higher risk of skin cancers, particularly non melanoma skin cancers and lymphoma, further increased by combined TNFα-antagonists (33, 34). A slightly increased risk of cervical abnormalities has also been suggested (33, 34). The few available evidences assessing the risk of new/recurrent cancer under thiopurines in IBD patients with previous cancer are encouraging (35), including a large meta-analysis in patients with a history of malignancy treated or untreated with thiopurines or other immunomodulators (36).Nevertheless, a careful evaluation of IBD

patients with a history of cancer is required before using thiopurines and drug discontinuation at diagnosis of cancer currently appears the initial option. Cancer type, time interval from diagnosis of cancer, age and IBD severity should be considered, with decision made on a patients' basis shared with oncologists and patients.

Evidence regarding the risk of new/recurrent cancer in IBD patients with present/prior cancer using methotrexate monotherapy is lacking and further studies are required. Not conclusive, but reassuring data derive using methotrexate in rheumatoid arthritis (36, 37).

TNF-α is a cytokine provided of several activities, including necrotic activity on cancer cells "*in vitro*." Several large independent studies support that TNF-inhibitors do not increase the overall cancer risk in IBD (33, 38–42). However, a slight excess risk of skin cancers, particularly melanoma, has been reported together with an increased risk of lymphoma particularly using combined thiopurines (43, 44). Whether TNFα-antagonists increase the risk of new/recurrent cancer in IBD patients with a diagnosis of cancer is being investigated. This analysis is currently limited by the small samples size of patients with specific cancer types. Additional limitations include differences among studies in terms of cancer stage, concomitant treatments, length of follow up and time interval from diagnosis of cancer to TNF-antagonists use. Despite these limitations, available preliminary evidence (mostly referring to overall cancer or melanoma) does not support that blocking TNFα increases the risk of new/recurrent cancer in IBD patients with prior cancer (36, 45, 46). As for other cancers, indication for TNF-antagonists in IBD patients with a history of cancer requires a careful selection of patients in a multidisciplinary approach with oncologists.
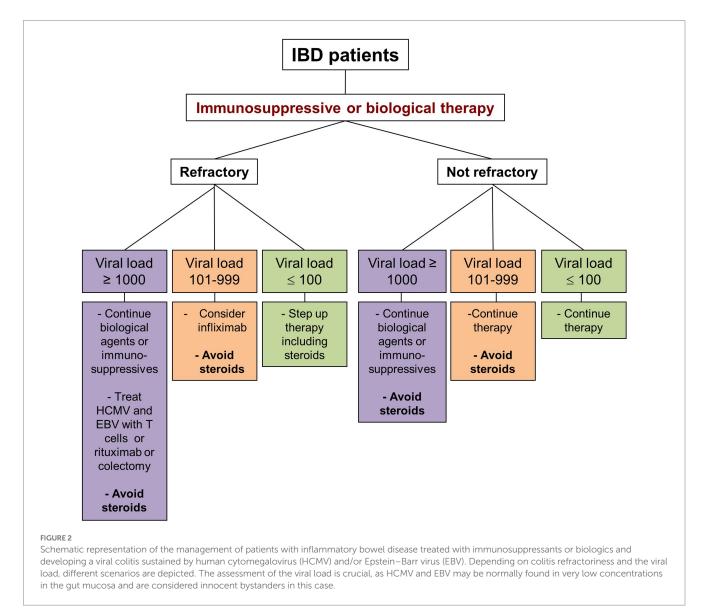
Vedolizumab (anti-α4β7 integrin) and ustekinumab (anti-IL-21/IL-23) have recently been used in IBD. Although a longer follow up is required, evidences suggest that their use does not increase the overall cancer risk in IBD (47, 48).In patients with a present or prior history of cancer, one retrospective study reported that vedolizumab does not increase the risk of new/recurrent cancer (49). Comparable findings were observed using vedolizumab or ustekinumab in IBD patients with prior malignancy (50). Additional data and a longer follow up is required for assessing the risk of new/recurrent cancer using these more immunomodulators, and particularly tofacitinib (pan-JAK inhibitor) (51) in IBD patients with a history of cancer.

Tailoring treatment of IBD in patients with superimposed viral infections

The main culprits of superimposed viral infection in IBD are human cytomegalovirus (HCMV, a β-herpesvirus) and Epstein–Barr virus (EBV, a ɣ-herpesvirus) (52, 53). They display the unique ability of establishing a lifelong latency (54–56) and reactivating in cases of reduced host immunity giving rise to systemic or end-organ disease (57, 58). Latent infection is the condition where viral genome is integrated with the host genome, viral gene expression is limited, and no virus is produced. The shift from latency to replication largely depends on T-cell immune control and/or changes in the differentiation/activation state of cells harboring viral genome (57, 58). While isolated reactivation events occur uneventfully in the immunocompetent host, critical stress or immunosuppression may trigger the lytic phase of the viral life cycle (57, 59). In this case, the

involvement of colonic mucosa in IBD patients (60, 61) makes challenging to distinguish between a relapse of the underlying disease and a superimposed viral colitis. Indeed, both the clinical picture and endoscopic features are similar and viral DNA in peripheral blood is detectable only in a minority of patients, while serology is unreliable. The measurement of mucosal viral load by quantitative real-time polymerase chain reaction allows not only to diagnose a superimposed viral colitis, but also to distinguish this condition from infection by applying the cut-off value of 1,000 copies/105 cells, as follows:

(a) viral colitis for values >103 copies/105 cells,
(b) reactivation of latent infection for values between 102 and 103 copies/105 cells,
(c) latent infection for values <102 copies/105 cells,
(d) systemic disease when detectable copies are found in peripheral blood together with viral colitis.

Indeed, both immunohistochemistry and *in situ* hybridization are poorly sensitive and even in case of positivity, they do not give any information about the state of virus replication (62). Moreover, a correct and timely therapeutic management depends on the stratification of patients accordingly to these value ranges (Figure 2) since in the case of viral colitis/systemic disease a quick tapering and discontinuation of steroid therapy is mandatory, since it favors viral replication (63), while it is only preferable in case of reactivation to avoid an overt viral colitis, and no modification is required in case of latent infection. As far as the underlying therapy with azathioprine or anti-tumor necrosis factor-α agents is regarded, their long-lasting therapeutic activity makes unnecessary their discontinuation, rather the ability of infliximab to reinduce T-cell apoptosis (64) may limit the activation of the viral lytic phase. By contrast, the effects of inhibitors of T-cell homing (such as anti-integrin monoclonal antibodies, modulators of sphingosine -phosphate receptor) are unpredictable since their use may hamper the number of effector memory T-cells that are largely responsible for the containment of virus-infected cells and virus replication (65). No data are available on the effects, if any, of small molecules (Janus kinase inhibitors) on EBV and HCMV reactivation in IBD patients. In addition, antiviral therapy with ganciclovir (5 mg/kg bid iv) for 4 weeks is recommended in those with HCMV disease (66), with monitoring of the mucosal viral load at the

FIGURE 2
Schematic representation of the management of patients with inflammatory bowel disease treated with immunosuppressants or biologics and developing a viral colitis sustained by human cytomegalovirus (HCMV) and/or Epstein−Barr virus (EBV). Depending on colitis refractoriness and the viral load, different scenarios are depicted. The assessment of the viral load is crucial, as HCMV and EBV may be normally found in very low concentrations in the gut mucosa and are considered innocent bystanders in this case.

end of treatment, while no effective treatment is available for EBV disease. The use of the anti-CD20 monoclonal antibody rituximab (375 mg/m^2 body surface iv weekly) (67) was tentatively applied, but the poorness of information does not allow to draw firm conclusion. The use of adoptive transfer of virus-specific cytotoxic T-cell clones (68) has great therapeutic potential, but it is limited to those centers with good manufacturing practice facility and approval by regulatory body is required. This strategy is even more important if considering that an impairment of EBV-specific T-cell immunity was shown in ulcerative colitis patients, mostly in those refractory to current therapy (69). Whether passive transfer of virus-specific antibodies or immunoglobulin preparations may help the immune system of IBD patients to recover the ability to silence viral replication deserves investigation. Finally, an increased risk of lymphoma has been found especially in young IBD males under thiopurines, where a role for primary EBV infection has been proposed (70). Therefore, it is mandatory to start this therapy only after positivity of EBV serology has been verified. In parallel, all those factors favoring viral reactivation, such as malnourishment, should be corrected.

Participate

How to communicate with IBD patients

An effective and adequate communication between patients and healthcare providers (HCP) constitutes a critical step in the management of IBD throughout the whole course of disease, indeed representing the foundation for a successful engagement in the decision-making process. As a matter of fact, playing an active role in the therapeutic strategies is ranked as "very important" by most of patients (71) and it is associated with a higher rate of satisfaction and adherence to therapy, as well as with improved clinical outcomes (72, 73). Education concerning the disease itself, its course, management, and prognosis starts at the time of diagnosis and requires a careful assessment of patients' needs, concerns, and level of awareness by HCP (74). At this phase, several barriers could influence the quality of the communication, such as the diagnostic delay responsible for patients' distrust in medicine and HCP, the difficult acceptance of a chronic disease and its potential impact on quality of life (75). A useful tool to assess patients' concern and to plan specific interventions accordingly, is represented by the rating form of IBD patient concerns (RFIPC), a 25-item questionnaire, requiring an individual score for the level of concern about several topics (e.g., cancer, specific symptoms, drug safety) (76). A survey from University of Manitoba, enrolling newly diagnosed IBD patients, showed that about 25% of them were dissatisfied with the amount of information received at the time of diagnosis, especially on specific issues such as long-term prognosis, infertility risk and inheritance, therapeutic management of clinical symptoms and impact on daily living activities (77). Similar findings also emerged from the UC Narrative Global Surveys, including both 2,100 UC patients and 1,254 physicians, showing an overall satisfying doctor-patient relationship; nevertheless, it is worth pointing out that up to 72% of patients wished they had received more information and support at the time of the diagnosis. Moreover, specific themes, in particular those ones related to emotional domains, seem to represent a taboo for almost half of patients. Of note, sexual health and sexual dysfunction are among the most neglected topics

during medical visits, for several generical barriers such as "lack of time" or "more urgent issue to discuss," but also embarrassment perceived by both actors and the inadequate physicians' competence on how to manage potential emerging problems (78, 79).

Among HCP, a key role for the establishment of an efficacious communication with patients is played by the IBD-nurses. In a study promoted by the Crohn's and Colitis UK organization, 1,081 young adults IBD patients (mean age 23.3 years) were asked to respond to an online questionnaire about several issues related to their disease, including the quality of communication with HCP. Gastroenterologists were shown to be the main source of information, especially at the time of diagnosis. However, IBD-nurses usually represented the first contact during a flare, ranked highest for the frequency of contacts and for the mean level of comfort in communication, compared to gastroenterologists ($p < 0.0001$) (80).

Moreover, IBD-nurses often represent the gatekeeper and filter on lots of information derived from the patients' online health information seeking (81).

A specific mention should be made in regard to the specific language adopted by physicians while communicating with patients about their health status and when addressing their specific concerns. In particular, the Food and Drug Administration presented some evidence-based practical advice for the communication of risk and benefits, including, among others: (1) avoiding excessive use of technical terms, which would increase the risk of misunderstanding and ineffective communication, (2) employing visual tools to ease the comprehension of particularly challenging issues, and (3) providing absolute risks – rather than relative risks – when discussing drug safety (82).

Disability in IBD

In IBD patients, the altered bowel functions and non-bowel related symptoms (83, 84) heavily impact on patients' work, social and home life activities, leading to various degrees of disability.

According to the World Health Organization (WHO) disability is defined as: "…any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being" (85).

Recent data demonstrate that up to 46.6% of IBD patients complain some form of disability (86); given its relevance, researchers and clinicians felt the need to standardize the definition and the tools for assessing disability. The IBD-disability index was developed in 2011 and includes different aspects of life, namely General health, Body functions, Body structures, Activities and participation, Environmental factors (87). Although, this index appeared a solid and reliable research tool, it is not administered with ease in daily practice. As such, in 2017, the most important items from this questionnaire were selected and entered in a new visual instrument, called IBD-Disk, a self-administered tool (88).

Indeed, disease clinical activity in both CD and UC significantly correlates with disability, CD having a greater impact than UC (86, 89). Disability also strongly correlates to surgeries, hospitalizations, corticosteroid or anti-TNF usage. The presence of extraintestinal manifestations, as well as anaemia, has a profound impact on patients' quality of life and disability as well (89). Patients with ileal pouch anal anastomosis had greater disability compared to UC patients with medically managed disease; female sex and having a public, rather

than private, health insurance were further detrimental factors (90, 91). Also, overweight/obesity, being a social worker or having the perception of the need for a psychotherapist were identified as markers for a higher disability (86).

IBD-related disability also has consequences on working life and productivity (92). A Spanish community-based study revealed that 32% of patients had an officially recognized disability degree, while 4.1% had a work-disability pension; again, markers of a severe and progressive disease were major drivers of disability (93). Eventually, disability causes work loss and absenteeism, but also presenteeism (94) and affects patients' perception of their working life (95). Indeed, work-related disability does have a detrimental impact on patients' productivity, careers and earnings, which is specifically relevant for the female sex (96).

To conclude, preventing disability should be one of our pivotal aims when managing IBD patients. Disease control and avoiding disease progression may be a proper starting point; still, disability is multifaceted and not fully reflected by disease activity parameters. A new challenge for the years to come is to incorporate disability scores in clinical practice and trials (97).

Stigmatization and resilience in IBD

Given the symptoms experienced by IBD patients and IBD-related treatments, it appears clear that stigmatization may constitute a major issue in this context (98–101). Stigmatization is defined as the identification of negative characteristics that distinguish a person as different and worthy of separation from their family, social, or working environments, leading to losing social status, discrimination, and isolation (102). The sigma "perceived" by patients over time may be "internalized," thus leading to the belief that stereotypes about their condition are true and adapt their life to this new situation (4, 103). While stigmatization has been extensively investigated in patients living with chronic conditions having a high social impact, as in the case of mental illnesses (102), HIV infection (103), and cancer (104), only over the last decade has stigmatization drawn attention in the IBD field. Stigmatization can be quantified through different scales. Taft et al. (105) proposed the perceived stigma scale (PSS) which was, however, adapted from the original PSS in irritable bowel syndrome (106). The PSS-IBD is a self-administered scale comprising 10 statements which refer to either significant others or health care professionals. According to a recent review (4), roughly 30 papers have looked at stigmatization in IBD so far, highlighting some key areas of intervention, including the work/school environment, sexual life, social relationships, depression and anxiety. As stigmatization does not seem to depend on age, sex, and IBD clinical activity (98), other factors should be investigated for tackling this issue.

The concept of stigmatization may be related to that of resilience (4), which is the ability to adapt well in the face of adversity, tragedy, threats or significant sources of stress (107). Hence, resilience is the ability to cope positively and to "bounce back" despite an adverse event, and this characteristic has been studied in patients with different chronic illnesses (108–110), a higher resilience being generally correlated with better outcomes. Several scales have been proposed, the most used being the 25-item Connor-Davidson resilience scale (CD-RISC) (111), validated into more than 70 different languages. Despite the availability of effective interventions (112), resilience has been poorly addressed in IBD (4), and

some results are contrasting. For example, in a recent Italian study (98), resilience was shown to be inversely related to disease activity in UC, but not in CD, while in a previous study from Korea (112), the clinical characteristics of UC did not affect resilience. Other factors that have been assessed in other studies are age, sex, disease characteristics, and social context, although with some limitations (4). The only study specifically looking at their mutual relationship found a significant—though modest—and inverse correlation between the two (98).

To conclude, stigmatization and resilience should be considered as important features in IBD patients. Future studies should investigate both their determinants and possible *ad-hoc* interventions for improving resilience and fighting stigmatization.

Quality of care standards in IBD

IBD is a spectrum of inflammatory chronic intestinal conditions which need a complex approach in regards of diagnosis, management and follow-up (113). Despite several guidelines (8, 11, 114, 115), the approach to IBD patients remains heterogeneous across countries and even in the same country, as it depends on several factors, such as access to healthcare system, reimbursement policies, expertise of healthcare professionals and knowledge of IBD by the general population. Therefore, a clear definition of standards of care (SoC), and objective outcome measures in IBD are needed.

The most recent version of a general definition of SoC "that which a minimally competent physician in the same field would do under similar circumstances" (116). Based on this definition, the European Crohn's Colitis Organisation (ECCO) decided to approach and define quality SoC by a Consensus process among expert healthcare professionals who are involved in the IBD management. The first step was to make a systematic review of the literature to identify the main domains of SoC in IBD. The panel identified three main domains: structure, processes, and outcomes (117). These results served as a basis to set up a list of statements which should identify the essential and desirable characteristics of the structure of an IBD unit, processes for diagnosis, treatment, and follow-up of IBD patients, and outcome to measure the quality of care. The final list of statements was voted during a Consensus meeting held in Copenhagen in 2019 by a multidisciplinary panel of experts and by the ECCO National Representatives, and published as an ECCO position paper (118). Because of the wide heterogeneity across countries and local situations, this position paper was intended to be a starting point for further definition of SoC in IBD that could be adopted, adapted or revised at national and local level. The ECCO is now planning a further step to harmonize SoC in Europe through the E-Quality project, which should identify gaps between the desired SoC and local reality in order to improve knowledge and remove barriers for a high-quality service for IBD patients (119).

Predict

Predicting relapse through faecal markers in IBD

IBD is characterized by dysregulated activity of gut-associated lymphoid tissue, leading to overly active intestinal inflammation. This,

in turn, leads to chronic inflammatory symptoms, including diarrhoea and abdominal pain, and possible progression toward bowel wall fibrosis and penetrating complications, i.e., fistula and abscesses (120).

Similarly, to other autoimmune conditions, despite maintenance treatment, IBD follow a relapsing–remitting course, as inflammatory flares are interspersed with periods of symptomatic remission. The possibility to predict in advance disease exacerbations would greatly help in the management of IBD patients, as anti-inflammatory therapy escalation before symptomatic flares could prevent their occurrence and potentially positively impact the course of the disease (120). Traditionally, endoscopy has been considered the technique of choice to achieve this goal, as endoscopic activity has been associated with both short and long-term clinical outcomes in UC and CD patients (121–123). Endoscopy, however, has several limitations, including costs, availability, and acceptability by patients, which prevent a more widespread use of this technique for the purpose of relapse prediction. Hence, several efforts have been made over the last few years to discover and validate biomarkers able to predict inflammatory flares in asymptomatic patients, both in UC and CD patients. In the latter clinical condition, a significant proportion of studies focused on the identification of biomarkers predicting post-operative endoscopic and clinical relapse, in order to replace the predominant role of endoscopy in this clinical setting. Even if initial studies suggested a potential role for circulating inflammatory markers, including C reactive protein (CRP) levels, in predicting relapse in asymptomatic patients with CD (124), the current focus has been put on faecal biomarkers, owning to their high specificity and reduced invasiveness.

Faecal biomarkers used in IBD are direct products of inflammatory cells which infiltrate the intestinal mucosa during disease activity. Calprotectin, a protein which constitute 60% of the cytosolic protein in human neutrophils, is a calcium binding heterocomplex of S100A8 and S100A9, whose stool levels are proportional to the influx of neutrophils into the gut lumen, and therefore closely reflects mucosal inflammation (125). Other neutrophil-derived proteins, i.e., faecal lactoferrin and S100A12, are currently being studied as a potential alternative to faecal calprotectin in IBD patients, even if additional studies will be needed to determine their comparative values. Nevertheless, a large number of studies have been carried out demonstrating that levels of these biomarkers, and particularly those of faecal calprotectin, significantly correlate with the endoscopic and histological activity in both UC and CD patients (126).

More than 30 studies have so far evaluated the role of faecal calprotectin in predicting clinical relapse in patients with quiescent IBD (127–136). These studies widely differ in terms of population enrolled, faecal calprotectin cut-off value and method used to assess its levels, follow-up duration and definition of relapse. These limitations explain the extreme heterogeneity of results obtained, as sensitivity and specificity values for predicting relapse range from 28 to 100% and 43 to 52% in CD, and from 31 to 100% and 63 to 100% in UC patients. By considering data from six studies, a meta-analysis by Mao et al. calculated a pooled sensitivity and specificity of faecal calprotectin in predicting relapse in quiescent IBD to be 78 and 73%, respectively, in 672 adult IBD patients (318 UC and 354 CD) (137). Similar figures were observed regarding the role of faecal calprotectin in predicting post-operative recurrence. In the POCER study, applying a faecal calprotectin threshold of 100 μg/g, sensitivity and specificity of this test for detecting a meaningful endoscopic relapse (i.e., endoscopic Rutgeerts' score ≥ 2) was 89 and 58%, respectively.

Authors of the study calculated that applying an algorithm based upon calprotectin values at 6 months following intervention could allow 41% of patients to avoid colonoscopy (138). In a meta-analysis performed by Tham et al., when a faecal calprotectin threshold of 150 μg/g was used, a pooled sensitivity and specificity for of 70 and 69%, respectively, was calculated in the post-operative setting (139). Indeed, the calprotectin cut-off to be used must consider several variables. First, there are differences between CD and UC. For CD, a cut-off of 250 μg/g discriminates disease activity and predicts disease flare (140). For UC, different cut-offs are able to discriminate remission (<150 μg/g), mild (150–200 μg/g), or moderate/severe (>200 μg/g) disease. Finally, according to a recent expert opinion, a cut-off of <40 μg/g indicates deep IBD remission (140).

Predicting response and toxicity to thiopurines in IBD

Thiopurines, azathioprine, 6-mercaptopurine and thioguanine, have long been used for the medical treatment of IBD (141–143). They have been shown to be effective in maintaining remission in patients with IBD, effectively helping to reduce the rate of surgery in both CD and UC patients, the post-operative relapse rate in CD and the risk of colorectal cancer associated with IBD. Furthermore, when used in combined therapy, they improve the pharmacokinetics of anti-TNF monoclonal antibodies (144). However, with the continuous advent of new biological therapies with different mechanisms of action, the role of thiopurines is being questioned (145).

Up to 20% of patients will respond inadequately or develop toxicity to thiopurine (146), requiring treatment interruption or modification. The availability of predictors for thiopurine response and toxicity allows us to customize this treatment for patients with IBD.

The ability to predict who will respond to thiopurine therapy and to maximize the likelihood of responding earlier in the course of the disease would allow clinicians to tailor therapy earlier, with the goal of altering the natural history of the disease.

Obviously, pre-treatment predictors would be the ideal way to personalize thiopurine therapy in IBD patients.

Several clinical predictors [intestinal site, body mass index, disease activity, disease duration, early or late introduction of thiopurines, ethnicity, sex, etc.] were explored with conflicting results (147). Thiopurine metabolites, thiopurine-S-methyltransferase [TPMT] activity, TPMT polymorphisms and deletion of GSTM1, a polymorphism of the gene encoding glutathione-S-transferase, the enzyme responsible for converting azathioprine in 6-mercaptopurine, they have been studied as predictors of response to thiopurine (147). The use of thiopurine is undoubtedly hindered by the high incidence of adverse drug reactions affecting up to 25% of people who take them, leading to discontinuation of the drug in 17% of patients (148). Side effects often occur in the first few months. Consequently, the ability to predict which patients might develop these potentially serious side effects would be of great use in clinical practice. Toxicities addressed will include myelotoxicity, hepatotoxicity, pancreatitis, alopecia, gastrointestinal and flu-like symptoms and complications associated with Epstein–Barr virus. Thus, while monitoring of thiopurine metabolites shows utility in those already initiated with thiopurine, pharmacogenetic tests, which already play a significant role in preventing toxicity, show some promise in predicting response.

Predicting response to biologics in IBD

Since the introduction of TNF-alpha inhibitors in the IBD therapeutic armamentarium, other monoclonal antibodies targeting different inflammatory mechanisms have been developed. Namely, vedolizumab targeting alpha4-beta7 integrin involved in T cell intestinal homing and ustekinumab blocking p40, a subunit shared by both by interleukin (IL) 12 and 23 are now available for patients.

Despite the increasing number of therapies available, a high rate of primary failure is observed. Overall, about 30–40% of patients do not respond to TNF inhibitors and those in which an initial clinical benefit is reached tend to lose response and experience clinical relapse over time (149, 150). Similar results have been observed with vedolizumab (151, 152) and ustekinumab (153, 154). In this situation patients are at risk of multiple therapeutic failures with an increased risk to develop complications and permanent organ damage due to uncontrolled inflammation. For these reasons, the identification of predictive factors describing the most appropriate patient for a specific mode of action is currently concentrating large part of research efforts in the IBD field.

Moving from the concept "one drug fits all" to a more personalized approach to patients, different putative predictive factors have been considered that can be divided in different subgroups: patient-related factors, disease-related factors, biomarkers, immune-system-related factors, and microbiota composition. Most of the association studies aiming at identifying predictive factors have been conducted in patients treated with TNF inhibitors and only few have been explored to predict response to vedolizumab and ustekinumab.

Age, gender, and body mass index as predictive factors of response to infliximab reported contrasting results with some studies reporting an association while other failed to do so (reviewed in (155)). Though well defined as risk factor for disabling disease in Crohn's disease (CD), the role of smoking in predicting response to anti-TNF agents is uncertain (156, 157).

As for disease characteristics, post-hoc analysis from anti-TNF agents registrative trials have found longer disease duration, fibro-stenosing behavior and ileal localization to be associated to worse outcome in anti-TNF-treated CD patients. Overall, the effect of these factors, although not systematically confirmed, might be reconducted to the progressive development of fibrotic ileal stenosis in long-standing CD, a condition that is unlikely to respond to any biologic therapy. Accordingly, the predictive role of these factors in UC is less defined (155).

Finally, biomarkers of inflammation such as CRP and faecal calprotectin have been associated in some studies to higher response rate to anti-TNF agents in CD (158–162) and UC (163–165). Whether more severe inflammation is required for anti-TNF agents to better exert their effect or CRP and faecal calprotectin merely support the presence of intestinal inflammation in patients otherwise affected by symptoms caused by other conditions (e.g., IBS) remains unclear.

While GWAS identified several gene variants associated with the increased risk to develop IBD and some of them were shown to be associated with specific disease phenotype and disease course severity, few have been linked to response to anti-TNF agents. Variants of genes involved in cell apoptosis have been associated to infliximab response while the low affinity immunoglobulin gamma Fc region receptor III-A (FCGR3A) and HLA-DQA1*05 were shown to be associated to antidrug antibody formation and secondary loss of response in CD (166, 167).

A few studies have also assessed the response to therapies in relation to anti-drug antibodies and trough levels, with conflicting results (168). In a previous study, the presence of anti-drug antibodies and low trough levels was predictive of early failure with biosimilar infliximab (169). In another, retrospective study, the baseline infliximab trough levels were not predictive of IBD relapse over the following 2 years (170). Hence, therapeutic drug monitoring for this purpose is uncertain.

In addition to the limited results obtained to identify patient predisposition to respond to biologics, genetic analysis does not consider the dynamic nature of the inflammatory process characterizing IBD. To identify factors that may influence response to therapy in a specific phase of IBD course, analysis of gene expression at mRNA and protein level in the peripheral blood and the intestinal mucosa have been performed. For instance, low expression levels of the triggering receptor expressed on myeloid cells (TREM-1) in the peripheral blood of IBD patients was predictive of primary non-response to anti-TNF therapy (171). However, in another independent CD cohort, downregulation of TREM-1 was predictive of mucosal healing (172). Similarly, serum and tissue expression of oncostatin M was also associated with primary non-response to infliximab and golimumab (173, 174). More recently the expression of membrane-bound TNF and alpha4-beta7 at mucosal level detected by fluorescent-adalimumab and vedolizumab in conjunction with confocal endomicroscopy was shown to predict response in small cohorts of patients treated with adalimumab and vedolizumab, respectively, (175, 176). Additionally, in a very recent study, prediction of response to biologics was assessed through a computerized image analysis of probe confocal laser endomicroscopy (pCLE) *in vivo* and by assessing the binding of fluorescent-labeled biologics *ex vivo* (177). The authors found an 85% and an 80% accuracy in predicting response to therapy in UC and CD, respectively. Additionally, a good prediction to response to anti-TNFs was noticed through a panel of expressed genes (AUC > 0.7).

Microbiota composition has been also explored as predictive factor of response to biologic therapy. Metagenomic analysis of stool samples from patients commencing vedolizumab therapy showed higher alpha-diversity and greater abundance of Roseburia inulinivorans and a Burkholderiales species in CD who achieved remission at week 14 (178). Interestingly, in this study the model incorporating metagenomic and clinical data performed better than the model considering metagenomic data alone.

Most of the aforementioned studies exploring potential predictive factors are biased by the limited number of patients analyzed and in most of the cases by the lack of a validation in a separate independent cohort of patients. The future will see the integration of datasets from different "omic" approaches, as in the case of the Endo-omic study (177), in addition to clinical characteristics in the attempt to define a reliable patient profile to predict response to biologics.

Prevent

Preventing flare-up and dysplasia through advanced endoscopy in IBD

Endoscopy is the gold standard for diagnosis, surveillance and assessment of luminal disease activity and extent in IBD patients (115). In recent years, several advanced endoscopic imaging and artificial intelligence techniques were introduced, allowing a detailed

analysis of the endoscopic images for precise and reproducible quantification of early inflammatory and dysplastic changes at a microscopic and ultrastructural level. Currently, the main goal of advanced endoscopy in IBD is the assessment of deep mucosal healing looking beyond the standard definition of endoscopic remission for early prevention of disease flare-up and tight drug monitoring (179, 180).

In 2020, the Picasso study, a large, international, multicenter, prospective trial, demonstrated that virtual chromoendoscopy can predict valuable clinical outcomes with the similar accuracy provided by histology in UC patients (181, 182). The same study group is now developing two different operator-independent AI systems to detect deep endoscopic remission on virtual chromoendoscopy video-images (183) and histologic remission on digitalized histological slides (184) to predict the risk of a flare-up at 12 months, hereby enabling clinicians of novel diagnostic tools and strategies for precise patient-tailored management.

In 2021, Bossuyt et al. have described two different endoscopic prototypes for computer-aided assessment of mucosal inflammation in UC introducing the firsts operator-independent scoring systems in the field of IBD. Both prototypes can be activated in real time, do not require contrast agents and are supported by computer-aided algorithms (machine learning algorithm) that as opposed to other types of artificial intelligence (likewise convolutional neural network) must be fed structured data and are not able to cope with unforeseen circumstances. The red density score (185) provides a quantitative assessment of disease activity based on the redness map and vascular pattern recognition, which correlates well with both endoscopic and histopathological disease activity. The second artificial intelligence-powered endoscope provides a single short wave-length monochromatic LED light illumination enabling a magnified visualization of inflammatory changes on the pericryptal vessels (186). This artificial intelligence system predicts histologic remission with higher accuracy (86%) as compared with standard endoscopic scoring systems (74% with Mayo endoscopic sub score, 79% with UC endoscopic index of severity). Larger studies and validation in independent cohorts are on the way to confirm the preliminary results obtained with these colonoscopy prototypes.

In 2022, Maeda et al. have described a novel artificial intelligence system working on endocytoscopy images able to predict clinical relapse during 12 months of follow-up in UC patients in clinical remission from a single referral Japanese center. The endocytoscope was integrated into the distal tip of a standard colonoscope to collect ultra-magnified images (×520) in real time. Notably, irrespective of the operator expertise, this AI system predicts clinical relapse better than expert assessment of endoscopic remission (Mayo endoscopic score ≤ 1) and comparably than expert assessment of endoscopic deep remission (Mayo endoscopic score = 0) or histologic remission. Other studies either based on recorded colonoscopy videos (187–189) or prospectively collected fixed images (190) have produced confirmatory evidence on the promising role of AI in refining mucosa activity assessment (187–189) to predict prognosis in UC patients (190).

The diagnosis of colorectal dysplastic changes in patients with longstanding IBD colitis or primary sclerosing cholangitis is still an unmet issue (191). Small but clinically relevant non pedunculated colorectal lesions are often overlooked during surveillance colonoscopy due to their subtle or inflammatory-like appearance (192). In addition, the optical characterization of neoplasia is still

challenging in IBD colitis, even using advanced endoscopic technology in expert hands (193). Within this context, the future goal of artificial intelligence is the detection and characterization of colitis-associated dysplasia at an early stage, revealing non advanced colorectal lesions when still suitable for curative endoscopic resection or for timely prophylactic surgery based on a patient-tailored multidisciplinary approach (194). The first artificial intelligence-assisted detection of colitis-associated neoplasia has been recently video-documented (195). However, the artificial intelligence systems successfully adopted for sporadic colorectal adenoma detection and characterization were not trained in active and post-inflammatory changes, and therefore need further developing in the setting of IBD.

Preventing infections in IBD

The treatment of IBD has been revolutionized in recent years by the increasing use of immunosuppressants, biologics and small molecules. Although these powerful drugs have proved effective in controlling disease activity, they can lead to a condition of immunosuppression, consequently increasing the risk of new infections or reactivation of latent infections (196). In this context, the evaluation of the immunological and serological status of patients with IBD is extremely useful in proposing adequate preventive measures against such infections, first of all vaccines (197).

In this sense, the guidelines of the Infectious Diseases Society of America distinguish patients with low- and high-level immunosuppression (198). This distinction is crucial in evaluating the advisability of immunizing patients using live vaccines.

According to various evidences, the main risk factors for opportunistic infections are advanced age (OR 3.0 for patients>50 years) (199) and the simultaneous use of multiple immunosuppressive drugs, since the transition from a single immunomodulator to combination therapy increases the relative risk of infections from 2.9 to 14.5 (200) Considering TNF-α inhibitors alone – which are in themselves sufficient to define high-level immunosuppression, as previously mentioned – the TREAT registry showed an increased risk of serious infections with these drugs (HR 1.47) (201). Regarding the risk of infections with new biological therapies approved in IBD, vedolizumab – a monoclonal gut-selective antibody that targets integrin α4β7 and ustekinumab a monoclonal antibody directed against the p40 subunit of IL-12 and IL-23 do not appear to be associated with important infectious complications (202, 203). Tofacitinib – an orally administered non-selective JAK inhibitor – is associated with an increased risk of herpes zoster infection in patients with IBD, with an observed incidence of 4 herpes zoster infections per 100 patient-years (204). In this regard, the availability of Shingrix®, a new recombinant non-live vaccine already approved for adults aged 50 and over against virus reactivation, could be of great help in patients who will be treated with Tofacitinib and future drugs of the same class (205).

All patients with IBD must be tested for the hepatitis C and B virus (HBsAg, anti-Hbs, anti-Hbc) to assess the infectious status (current, past, inactive carrier) or vaccination status. In patients with evidence of active HBV infection, HBeAg, anti-HBe and HBV DNA must also be evaluated (206). Obviously, the HBV vaccine is recommended in all seronegative patients.

In patients who will be treated with TNF-α inhibitors, a careful preliminary assessment of the presence of latent tuberculosis is mandatory, since there is a high risk of reactivation of the infection with these drugs (207). If treatment with thiopurines is planned, screening should be performed to ascertain the serological status against EBV (208, 209).

Studies conducted in women with IBD demonstrated a high frequency of Human Papilloma Virus (HPV) associated Pap-smears abnormalities (210). In this setting, immunosuppressive drugs could increase the risk of persistent HPV infection and ultimately cervical cancer.

Infections caused by Neisseria meningitidis can evolve into a disease with high mortality, if not recognized and promptly treated. Meningococcal infections are endemic in Western countries, and the annual incidence of invasive meningococcal disease varies in multiyear cycles (211, 212).

The ongoing pandemic of COVID-19 caused by infection with SARS-CoV-2 is worthy of a brief comment in the context of vaccinations for patients with IBD. COVID-19 has raised substantial concerns for patients with IBD who are receiving immunosuppressive agents. Patients with IBD do not appear to be at greater risk of infection by SARS-CoV-2 compared to the general population, and current treatments are not associated with worse prognosis. However, clinicians should be cautious about the use of systemic steroids for treatment of COVID-19 (213).

Recently, a consensus on be-half of the International Organization for the Study of Inflammatory Bowel Disease provided several statements supporting SARS-CoV-2 vaccination in patients with IBD regardless the immune-modifying therapies (214). Generally, all IBD patients should be vaccinated for the following diseases: tetanus, diphtheria and polio, measles, mumps and rubella, HBV, influenza, varicella, HPV, pneumococcus, and meningococcus (215).

Physicians, and in particular gastroenterologists, should be encouraged to conduct a structured interview of all IBD patients at diagnosis, about the immunization status and the definition of a vaccination plan before the start of immunosuppressive treatment (215).

Preventing post-surgical recurrence in IBD

Only 10 years ago, the idea that a surgeon should be involved in the prevention of post-surgical recurrence of IBD would have been at least considered imaginative, but nowadays surgery has great an impact on the patients' clinical history, including the disease recurrence.

In UC surgery is curative, even if in very selected cases, a segmental colectomy could be considered to avoid total proctocolectomy (216). However, the patient could experience post-surgical consequences such as incisional hernias, stenosing or fistulizing complications of the ileo-pouch-anal anastomosis, and adhesions potentially causing obstructions and reduced fertility in women. The standardization of restorative proctocolectomy procedure, taking into account all the problems emerged during the past years of surgical practice, and the new technologies available, have significantly reduced all the major drawbacks, in particular, the long-term pouch disfunction and failure, giving the patients the possibility to avoid definite ileostomy (217–219). The extended use of

laparoscopy in referral centers has not only drastically reduced perioperative complications, length of hospitalization, and incisional hernias, but it left the women's fertility preserved through a notable reduction in adhesions (219–222). It is worth pointing out that laparoscopy can be used to complete a restorative proctocolectomy even in case of staged procedures, with very low conversion rate (220).

Looking at the other side of the IBD-moon, in the "traditional" view of CD clinical history, surgeons were only involved when any pharmacological option had been failed and perforating, or stenotic complications had been occurred. Due to this gastroenterologists' "last-resort" approach, the surgeons, for their part, have tried to focus on identifying all the risk factors for post-operative complications that they could have acted upon. Thanks to the evidence from surgical trials, performed at the turn of the 21st century, today we know that steroids and anti-TNF agents should be withdrawn before surgery, nutritional status checked and amended, deep venous thrombosis prevented, intra-abdominal abscesses radiologically drained, and acute obstruction managed conservatively, exploiting a "postpone and optimize" strategy (223). Furthermore, some risk factor for post-operative recurrence has been identified such as a genetic predisposition, a paediatric diagnosis, the need for surgery within 1 year of diagnosis, a smoking habit, a penetrating disease behavior in the terminal ileum and colon, a stricturing behavior associated with upper gastrointestinal location, the presence of perianal disease, and the bowel wall thickening and the endoscopic recurrence within 1 year after surgery (224–228). However, focusing on anastomotic post-surgical recurrence using the score proposed by Rutgeerts and colleagues, it became evident that different anastomotic configurations presented different long-term recurrence, with side-to-side anastomosis (either isoperistaltic or anisoperistaltic – also known as functional end-to-end) having the better results over all the other anastomotic configurations (end-to-side, end-to-end, and side-to-side with blind loops) (223, 229). Recently, a particular kind of functional end-to-end anastomosis, proposed by Kono et al., has been claimed to drastically reduce both post-operative complications and long term endoscopic and surgical recurrence, but a direct comparison with a stapled similar anastomosis, considering also postoperative adjuvant treatment, is still lacking (230, 231). Another argument of actual debate is the treatment of the mesentery during ileo-colic retention, since a group from Limerick supported a role of mesentery removal in preventing post-surgical recurrence. On the one hand, the well-known low recurrence rate observed on the site of a strictureplasty, a technique where both the diseased bowel and mesentery are preserved, is in stark contrast with this hypothesis (222, 224). On the other hand, a large retrospective study and a retrospective comparative analysis, both performed on prospective databases, failed to find any evidence and strengthened the importance of post-operative prophylaxis with biological treatment (231–234).

Unmet needs in IBD

Despite the recent developments in the diagnosis and monitoring of IBD (235–237), together with the new biologics and small molecules which expanded our therapeutic armamentarium for treating these diseases (238–240), several patients still suffer from disabling bowel symptoms and relevant disease complications (241, 242). Moreover, patients with IBD experience impairment of health-related quality of

life, fatigue, depression, and anxiety (243, 244). Thus, many questions remain to improve the management of IBD.

Both CD and UC are heterogeneous diseases, with significant differences in terms of disease location, activity, onset and course in each patient. However, current treatment strategies suggest a standard approach to all patients, because of the limited evidence regarding the existence of useful and easy-to-use predictors of response to therapy (245). In the last decade, with the novel drugs available, various efforts have been made to fill this gap, by evaluating the individual and molecular specificities of the disease, identifying new biomarkers and stratifying individual patients' risk factors in its early stages (246). Nevertheless, the incorporation of these predictors in routine clinical practice is not yet established.

IBDs are progressive disorders in which chronic inflammation may lead to disease progression, disability and complications (247–250). Various studies have shown that early use of biologic drugs is associated with improved clinical outcomes and, therefore, the accurate identification of patients who may benefit of early intervention seems to be crucial. Although several studies identified and suggested biochemical markers (e.g., faecal calprotectin, C-reactive protein, oncostatin M), clinical indices (i.e., early disease onset, smoking, use of steroids, extended disease, perianal involvement), genetic tests, proteomic, metabolomic or metagenomic and radiomics or imaging-based biomarkers, to identify higher-risk patients, prospective outcome data corroborating these variables are lacking. Thus, more objective and prospectively validated biomarkers are needed in order to implement a precision-medicine approach in IBD (246).

To date, registration trials demonstrated that current available treatments for both UC and CD do not achieve remission rates over 50%, underlining a therapeutic ceiling in the management of both diseases and potential challenges that need to be addressed (251). For this reason, a treat-to-target approach with tight monitoring of the disease during maintenance treatment has been investigated, emphasizing the potential to improve drug efficacy, but also highlighting the fact that patients still may present with complications in at least 30% of the cases in the mid-term (252). Moreover, treatment goals are challenging to achieve in clinical practice since they depend on many variables, including the disease duration, timing of treatment initiation, drugs available, compliance to treatment, and duration of therapy. Therefore, new and more effective therapies for IBD are needed. On the other hand, other questions arise from the use of current available treatments: which drug should be used as first-line treatment, which drug should be used after a failure, when to start or stop a drug, how to best adjust timing and dosing (i.e., the role of therapeutic drug monitoring). Moreover, should we combine biologics and small molecules to improve the efficacy without taking into consideration safety issues? Unfortunately, to date most of the comparative efficacy data can be retrieved from systematic reviews and network meta-analyses because head-to-head trials are in their early development (253, 254), whereas evidence regarding the combined use of drugs with different mechanisms of action is very limited and the risk-safety and cost–benefit analyses are still unsatisfactory (255).

There are other different clinical scenarios where there is a lack of evidence regarding the correct management of IBD. For instance, for the treatment of perianal fistulizing CD, infliximab represents the best-studied drug showing a long-term healing rate lower than 50%, while vedolizumab and ustekinumab have been only evaluated in retrospective studies and post-hoc analyses (256). Limited evidence is also available for the use of anti-JAK, mesenchymal stem cells, and combination of biological therapies in this setting. Likewise, the treatment of acute severe UC suffers from the same limitations mentioned above for perianal fistulizing CD, with a few treatment modalities assessed to date (257). Ulcerative proctitis (UP) represents another example of difficult-to-treat disease, since approximately half of these patients are refractory to conventional medical treatment and the efficacy data from registration biologic trials, where UP patients are systematically excluded, is limited (258). Prevention of post-operative recurrence is still a controversial field, although a recent systematic review and meta-analysis showed that anti-TNF therapies, alone or in combination, seem to be the best way for preventing endoscopic recurrence (259). However, which patients should be treated, the best timing to initiate biologic therapy in the post-operative setting, as well as the role of new biologic therapies, are all features that need to be investigated. Further, there is an urgent need to identify new therapeutic targets and new effective molecules for tackling intestinal fibrosis in CD. The uncertainties regarding the potential detrimental effects of such drugs for CD (i.e., perforation, worsening of intestinal inflammation) (3). In fact, there are no available therapies for this purpose, and, for this reason, the rate of surgery in CD is still high.

Also the frail patient, usually having an age over 65 years, with various comorbidities including the cardiovascular ones, represents a challenging clinical situation, since the high risk of developing significant adverse events (i.e., infections) leads frequently to adopt sub-optimal IBD therapy, as shown by chronic corticosteroid use and elevated surgical rates (260). In this type of patient, the use of gut-selective immunosuppressants seems to have the potential to reduce the risk of adverse events, but further studies are needed. Finally, other settings requiring further data and advancements are relative to the use of novel non-invasive markers for monitoring the disease, with a better correlation with mucosal inflammation and disease progression, and the improved control of fatigue together with anxiety and depression which are able to affect greatly the disease course and therefore should be considered in its management (261).

Conclusions and outlook

Due to its multifactorial pathogenesis, its clinical manifestations, and its long-life clinical impact, IBD represents a typical example of a complex disease (7), making its clinical management challenging for physicians. As we have discussed, age- and gender-specific issues, specific comorbidities, availability of different biologics and small molecules with different route of administrations, and socioeconomic and cultural factors, are just some of the variables that affect decision-making in IBD. Additionally, despite the availability of novel drugs, clinical and endoscopic remission rates on a long-term are still poor and proper drug positioning is uncertain. Hence, an integrated effort is required to meet the key objectives needed to pursue targeted treatment. The 4P framework seems to be the best currently available tool for clinicians that could be applied for tailoring interventions in day-by-day clinical practice in the IBD field. Table 2 summarises the main variables to be considered in the 4P medicine framework that could prove useful in the overall IBD management, along with a possible future trend per each area.

TABLE 2 Main variables to be considered in the 4P medicine framework that could prove useful in the overall management of inflammatory bowel disease (IBD).

4P sub-area	Variables to be considered	Future trends
Personalize	Age groups (i.e., childhood, adulthood, elderly) Sex and gender (i.e., male, female, cisgender, transgender, others) Co- and multi-morbidity Specific patient populations (i.e., pregnancy, oncological, immunosuppressed) Socioeconomic status in relation to coping abilities, disease understanding, impact on work-life balance Adherence to medications Patients' preferences	Research will focus on groups that are usually underrepresented in both clinical trials and observational studies Both sex and gender will be included and separately analyzed in clinical trials Real-world, controlled studies are warranted to study the safety and efficacy of the available drugs for treating IBD Patient-reported outcome always included in prospective studies
Participate	Communication with IBD patients Facing physical, psychological, and sexual disability Resilience and stigmatization Patient associations and public social events	Physician will be trained on how to communicate to IBD patients, as well as on how to assess disability, resilience, and stigmatization Patients will be more involved in public social events for raising awareness on IBD
Predict	Prediction of likelihood of developing IBD Prediction of likelihood of developing IBD complications Prediction of response to IBD treatment	Artificial intelligence and machine learning will allow early prediction of developing IBD and its complication and will allow a personalized approach to therapies More serum and faecal markers will be made available
Prevent	Prevention of disease flare or recurrence and dysplastic/neoplastic complications Prevention of opportunistic and vaccine-preventable infections Prevention of infertility/sexual issues, disability, and psychiatric illness deriving from IBD	Advanced endoscopic techniques will be made available for early detection of dysplasia and colorectal cancer Safe and new vaccine, also including the novel mRNA-based vaccines, will be made available and specifically tested in the IBD population Prevention of infertility and sexual issues, or of any other form of disability and psychological distress, will be key in the overall management of IBD patients

In the future, new tools for predicting important disease outcomes may become available and are eagerly awaited. Particularly, classical statistics, such as linear regression or advanced regression analyses, may fail to capture a meaningful sense of all the variables called into question in IBD. In fact, the increase in data complexity makes classical statistical inference less tractable (262). Recent advancements in the research field of machine learning have fostered the development and deployment of healthcare-focused algorithms. In this context, historical patient data are used to draw correlations and build machine learning models able to predict, with a known confidence, what is likely to happen to a patient, given their current medical condition. The use of artificial intelligence algorithms (263) may be able to capture and decipher complex, nonlinear relationships, that otherwise would be left unconsidered, and could be consider as an upgrade of the 4P medicine. So far, the only application of artificial intelligence in the field of IBD is that of endoscopy, field in which it proved useful in detecting preneoplastic alterations (264). A broader clinical application of artificial intelligence should be sought in future studies.

Author contributions

MVL and ADS introduction, conclusions, and outlook. MLS tailoring treatment of IBD in pregnant women. LB tailoring treatment of IBD in cancer patients. RC tailoring treatment of IBD in patients with superimposed viral infections. DP how to communicate with IBD patients. LP disability in IBD. MVL stigmatization and resilience in IBD. GF quality of care standards in IBD. FC predicting relapse through

faecal markers in IBD. SA predicting response and toxicity to thiopurines in IBD. MF predicting response to biologics in IBD. GT preventing flare-up and dysplasia through advanced endoscopy in IBD. AO preventing infections in IBD. GMS preventing post-surgical recurrence in IBD. ES unmet needs in IBD. GC, MVL, ADS, RD'I, MD, MV, GM, AK, and GCS overview and revision for important intellectual contents. All authors contributed to the article and approved the submitted version.

Conflict of interest

ES has served as speaker for Abbvie, AGPharma, Alfasigma, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Unifarco; has served as consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Falk, Fresenius Kabi, Janssen, Merck & Co, Reckitt Benckiser, Regeneron,

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn's disease. *Nat Rev Dis Primers*. (2020) 6:22. doi: 10.1038/s41572-020-0156-2

2. Kobayashi T, Siegmund B, Le Berre C, Wei SC, Ferrante M, Shen B, et al. Ulcerative colitis. *Nat Rev Dis Primers*. (2020) 6:74. doi: 10.1038/s41572-020-0205-x

3. Lenti MV, Di Sabatino A. Intestinal fibrosis. *Mol Asp Med*. (2019) 65:100–9. doi: 10.1016/j.mam.2018.10.003

4. Lenti MV, Cococcia S, Ghorayeb J, Di Sabatino A, Selinger CP. Stigmatisation and resilience in inflammatory bowel disease. *Intern Emerg Med*. (2020) 15:211–23. doi: 10.1007/s11739-019-02268-0

5. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol Hepatol*. (2020) 5:17–30. doi: 10.1016/S2468-1253(19)30333-4

6. Al-Bawardy B, Shivashankar R, Proctor DD. Novel and emerging therapies for inflammatory bowel disease. *Front Pharmacol*. (2021) 12:651415. doi: 10.3389/fphar.2021.651415

7. Corazza GR, Formagnana P, Lenti MV. Bringing complexity into clinical practice: an internistic approach. *Eur J Intern Med*. (2019) 61:9–14. doi: 10.1016/j.ejim.2018.11.009

8. Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis*. (2022) 16:2–17. doi: 10.1093/ecco-jcc/jjab178

9. Spinelli A, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, et al. ECCO guidelines on therapeutics in ulcerative colitis: surgical treatment. *J Crohns Colitis*. (2022) 16:179–89. doi: 10.1093/ecco-jcc/jjab177

10. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, et al. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis*. (2020) 14:155–68. doi: 10.1093/ecco-jcc/jjz187

11. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. (2020) 14:4–22. doi: 10.1093/ecco-jcc/jjz180

12. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. *Per Med*. (2013) 10:565–76. doi: 10.2217/pme.13.57

13. Gallinger ZR, Rumman A, Nguyen GC. Perceptions and attitudes towards medication adherence during pregnancy in inflammatory bowel disease. *J Crohns Colitis*. (2016) 10:892–7. doi: 10.1093/ecco-jcc/jjw052

14. Bortoli A, Pedersen N, Duricova D, Dinca R, Gionchetti P, Panelli MR, et al. European Crohn-colitis organisation (ECCO) study Group of Epidemiologic Committee (EpiCom). Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Aliment Pharmacol Ther*. (2011) 34:724–34. doi: 10.1111/j.1365-2036.2011.04794.x

15. Mahadevan U, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, et al. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD parenthood project working group. *Gastroenterology*. (2019) 156:1508–24. doi: 10.1053/j.gastro.2018.12.022

16. van der Woude CJ, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, et al. European Crohn's and colitis organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis*. (2015) 9:107–24. doi: 10.1093/ecco-jcc/jju006

17. Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al. The Toronto consensus statements for the Management of Inflammatory Bowel Disease in pregnancy. *Gastroenterology*. (2016) 150:734–757.e1. doi: 10.1053/j.gastro.2015.12.003

18. Italian Group for the Study of Inflammatory Bowel Disease Working GroupArmuzzi A, Bortoli A, Castiglione F, Contaldo A, Daperno M, et al. Female reproductive health and inflammatory bowel disease: a practice-based review. *Dig Liver Dis*. (2022) 54:19–29. doi: 10.1016/j.dld.2021.05.020

19. Odufalu FD, Long M, Lin K, Mahadevan U PIANO investigators from the Crohn's and colitis foundation (CCF) clinical research Alliance recruited patients for their respective centers for participant enrollment. Exposure to corticosteroids in pregnancy is associated with adverse perinatal outcomes among infants of mothers with inflammatory bowel disease: results from the PIANO registry. *Gut*. (2021) 71:1766–72. doi: 10.1136/gutjnl-2021-325317

20. Kanis SL, de Lima-Karagiannis A, de Boer NKH, van der Woude CJ. Use of Thiopurines during conception and pregnancy is not associated with adverse pregnancy outcomes or health of infants at one year in a prospective study. *Clin Gastroenterol Hepatol*. (2017) 15:1232–1241.e1. doi: 10.1016/j.cgh.2017.02.041

21. Mahadevan U, Long MD, Kane SV, Roy A, Dubinsky MC, Sands BE, et al. Pregnancy and neonatal outcomes after fetal exposure to biologics and Thiopurines among women with inflammatory bowel disease. *Gastroenterology*. (2021) 160:1131–9. doi: 10.1053/j.gastro.2020.11.038

22. Branche J, Cortot A, Bourreille A, Coffin B, de Vos M, de Saussure P, et al. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis*. (2009) 15:1044–8. doi: 10.1002/ibd.20858

23. Nielsen OH, Gubatan JM, Juhl CB, Streett SE, Maxwell C. Biologics for inflammatory bowel disease and their safety in pregnancy: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2022) 20:74–87.e3. doi: 10.1016/j.cgh.2020.09.021

24. Lichtenstein GR, Feagan BG, Mahadevan U, Salzberg BA, Langholff W, Morgan JG, et al. Pregnancy outcomes reported during the 13-year TREAT registry: a descriptive report. *Am J Gastroenterol*. (2018) 113:1678–88. doi: 10.1038/s41395-018-0202-9

25. Chaparro M, Verreth A, Lobaton T, Gravito-Soares E, Julsgaard M, Savarino E, et al. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. *Am J Gastroenterol*. (2018) 113:396–403. doi: 10.1038/ajg.2017.501

26. Moens A, van Hoeve K, Humblet E, Rahier JF, Bossuyt P, Dewit S, et al. Outcome of pregnancies in female patients with inflammatory bowel diseases treated with Vedolizumab. *J Crohns Colitis*. (2019) 13:12–8. doi: 10.1093/ecco-jcc/jjy142

27. Bar-Gil Shitrit A, Ben Ya'acov A, Livovsky DM, Cuker T, Farkash R, Hoyda A, et al. Exposure to Vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. *Am J Gastroenterol*. (2019) 114:1172–5. doi: 10.14309/ajg.0000000000000186

28. Moens A, van der Woude CJ, Julsgaard M, Humblet E, Sheridan J, Baumgart DC, et al. Pregnancy outcomes in inflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: results of the European CONCEIVE study. *Aliment Pharmacol Ther*. (2020) 51:129–38. doi: 10.1111/apt.15539

29. Wils P, Seksik P, Stefanescu C, Nancey S, Allez M, Pineton de Chambrun G, et al. Safety of ustekinumab or vedolizumab in pregnant inflammatory bowel disease patients: a multicentre cohort study. *Aliment Pharmacol Ther*. (2021) 53:460–70. doi: 10.1111/apt.16192

30. Chaparro M, Gutiérrez A, Calviño-Suárez C, Huguet JM, Calvo M, Aguas M, et al. Safety of ustekinumab in pregnant patients with inflammatory bowel disease and their offspring: results from the DUMBO registry of GETECCU. *J Crohns Colitis*. (2022) 16:i491–3. doi: 10.1093/ecco-jcc/jjab232.672

31. Clowse ME, Feldman SR, Isaacs JD, Kimball AB, Strand V, Warren RB. Pregnancy outcomes in the Tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf*. (2016) 39:755–62. doi: 10.1007/s40264-016-0431-z

32. Mahadevan U, Dubinsky MC, Su C, Lawendy N, Jones TV, Marren A, et al. Outcomes of pregnancies with maternal/paternal exposure in the Tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. (2018) 24:2494–500. doi: 10.1093/ibd/izy160

33. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med*. (2015) 372:1441–52. doi: 10.1056/NEJMra1403718

34. Annese V, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, et al. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis*. (2015) 9:945–65. doi: 10.1093/ecco-jcc/jjv141

35. Beaugerie L, Carrat F, Colombel JF, Bouvier AM, Sokol H, Babouri A, et al. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. *Gut*. (2014) 63:1416–23. doi: 10.1136/gutjnl-2013-305763

36. Shelton E, Laharie D, Scott FI, Mamtani R, Lewis JD, Colombel JF, et al. Cancer recurrence following immune-suppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. *Gastroenterology*. (2016) 151:97–109.e4. doi: 10.1053/j.gastro.2016.03.037

37. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis*. (2009) 68:1100–4. doi: 10.1136/ard.2008.093690

38. Biancone L, Orlando A, Kohn A, Colombo E, Sostegni R, Angelucci E, et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut*. (2006) 55:228–33. doi: 10.1136/gut.2005.075937

39. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Langholff W, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ registry. *Am J Gastroenterol*. (2014) 109:212–23. doi: 10.1038/ajg.2013.441

40. Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. (2016) 14:1385–1397.e10. doi: 10.1016/j.cgh.2016.04.039

41. Nyboe Andersen N, Pasternak B, Basit S, Andersson M, Svanström H, Caspersen S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. *JAMA*. (2014) 311:2406–13. doi: 10.1001/jama.2014.5613

42. Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. (2014) 39:447–58. doi: 10.1111/apt.12624

43. Singh S, Nagpal SJ, Murad MH, Yadav S, Kane SV, Pardi DS, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2014) 12:210–8. doi: 10.1016/j.cgh.2013.04.033

44. Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. (2011) 9:36–41.e1. doi: 10.1016/j.cgh.2010.09.016

45. Axelrad J, Bernheim O, Colombel JF, Malerba S, Ananthakrishnan A, Yajnik V, et al. Risk of new or recurrent cancer in patients with inflammatory bowel disease and previous cancer exposed to immunosuppressive and anti-tumor necrosis factor agents. *Clin Gastroenterol Hepatol*. (2016) 14:58–64. doi: 10.1016/j.cgh.2015.07.037

46. Poullenot F, Seksik P, Beaugerie L, Amiot A, Nachury M, Abitbol V, et al. Risk of incident cancer in inflammatory bowel disease patients starting anti-TNF therapy while having recent malignancy. *Inflamm Bowel Dis*. (2016) 22:1362–9. doi: 10.1097/MIB.0000000000000741

47. Card T, Ungaro R, Bhayat F, Blake A, Hantsbarger G, Travis S. Vedolizumab use is not associated with increased malignancy incidence: GEMINI LTS study results and post-marketing data. *Aliment Pharmacol Ther*. (2020) 51:149–57. doi: 10.1111/apt.15538

48. Sandborn WJ, Feagan BG, Danese S, O'Brien CD, Ott E, Marano C, et al. Safety of Ustekinumab in inflammatory bowel disease: pooled safety analysis of results from phase 2/3 studies. *Inflamm Bowel Dis*. (2021) 27:994–1007. doi: 10.1093/ibd/izaa236

49. Vedamurthy A, Gangasani N, Ananthakrishnan AN. Vedolizumab or tumor necrosis factor antagonist use and risk of new or recurrent cancer in patients with inflammatory bowel disease with prior malignancy: a retrospective cohort study. *Clin Gastroenterol Hepatol*. (2022) 20:88–95. doi: 10.1016/j.cgh.2020.10.007

50. Hong SJ, Zenger C, Pecoriello J, Pang A, Vallely M, Hudesman DP, et al. Ustekinumab and Vedolizumab are not associated with subsequent cancer in IBD patients with prior malignancy. *Inflamm Bowel Dis*. (2022) 28:1826–32. doi: 10.1093/ibd/izac035

51. Sandborn WJ, Lawendy N, Danese S, Su C, Loftus EVJr, Hart A, et al. Safety and efficacy of tofacitinib for treatment of ulcerative colitis: final analysis of OCTAVE open, an open-label, long-term extension study with up to 7.0 years of treatment. *Aliment Pharmacol Ther*. (2022) 55:464–78. doi: 10.1111/apt.16712

52. Vega R, Bertrán X, Menacho M, Domènech E, Moreno de Vega V, Hombrados M, et al. Cytomegalovirus infection in patients with inflammatory bowel disease. *Am J Gastroenterol*. (1999) 94:1053–6. doi: 10.1111/j.1572-0241.1999.01013.x

53. Yanai H, Shimizu N, Nagasaki S, Mitani N, Okita K. Epstein-Barr virus infection of the colon with inflammatory bowel disease. *Am J Gastroenterol*. (1999) 94:1582–6. doi: 10.1111/j.1572-0241.1999.01148.x

54. Jarvis MA, Nelson JA. Human cytomegalovirus persistence and latency in endothelial cells and macrophages. *Curr Opin Microbiol*. (2002) 5:403–7. doi: 10.1016/s1369-5274(02)00334-x

55. Sinclair J. Human cytomegalovirus: latency and reactivation in the myeloid lineage. *J Clin Virol*. (2008) 41:180–5. doi: 10.1016/j.jcv.2007.11.014

56. Thorley-Lawson DA, Hawkins JB, Tracy SI, Shapiro M. The pathogenesis of Epstein-Barr virus persistent infection. *Curr Opin Virol*. (2013) 3:227–32. doi: 10.1016/j.coviro.2013.04.005

57. Loewendorf A, Benedict CA. Modulation of host innate and adaptive immune defenses by cytomegalovirus: timing is everything. *J Intern Med*. (2010) 267:483–501. doi: 10.1111/j.1365-2796.2010.02220.x

58. Murata T, Tsurumi T. Switching of EBV cycles between latent and lytic states. *Rev Med Virol*. (2014) 24:142–53. doi: 10.1002/rmv.1780

59. Vogl BA, Fagin U, Nerbas L, Schlenke P, Lamprecht P, Jabs WJ. Longitudinal analysis of frequency and reactivity of Epstein-Barr virus-specific T lymphocytes and their association with intermittent viral reactivation. *J Med Virol*. (2012) 84:119–31. doi: 10.1002/jmv.22258

60. Sager K, Alam S, Bond A, Chinnappan L, Probert CS. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther*. (2015) 41:725–33. doi: 10.1111/apt.13124

61. Ryan JL, Shen YJ, Morgan DR, Thorne LB, Kenney SC, Dominguez RL, et al. Epstein-Barr virus infection is common in inflamed gastrointestinal mucosa. *Dig Dis Sci*. (2012) 57:1887–98. doi: 10.1007/s10620-012-2116-5

62. Ciccocioppo R, Racca F, Paolucci S, Campanini G, Pozzi L, Betti E, et al. Human cytomegalovirus and Epstein-Barr virus infection in inflammatory bowel disease: need for mucosal viral load measurement. *World J Gastroenterol*. (2015) 21:1915–26. doi: 10.3748/wjg.v21.i6.1915

63. Forbes BA, Bonville CA, Dock NL. The effects of a promoter of cell differentiation and selected hormones on human cytomegalovirus infection using an in vitro cell system. *J Infect Dis*. (1990) 162:39–45. doi: 10.1093/infdis/162.1.39

64. Kirman I, Whelan RL, Nielsen OH. Infliximab: mechanism of action beyond TNF-alpha neutralization in inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. (2004) 16:639–41. doi: 10.1097/01.meg.0000108345.41221.c2

65. Sylwester AW, Mitchell BL, Edgar JB, Taormina C, Pelte C, Ruchti F, et al. Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects. *J Exp Med*. (2005) 202:673–85. doi: 10.1084/jem.20050882

66. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The third international consensus guidelines on the Management of Cytomegalovirus in solid-organ transplantation. *Transplantation*. (2018) 102:900–31. doi: 10.1097/TP.0000000000002191

67. Green M, Michaels MG. Epstein-Barr virus infection and posttransplant lymphoproliferative disorder. *Am J Transplant*. (2013) 13:41–54. doi: 10.1111/ajt.12004

68. Keller MD, Bollard CM. Virus-specific T-cell therapies for patients with primary immune deficiency. *Blood*. (2020) 135:620–8. doi: 10.1182/blood.2019000924

69. Ciccocioppo R, Mengoli C, Betti E, Comolli G, Cassaniti I, Piralla A, et al. Human cytomegalovirus and Epstein-Barr virus specific immunity in patients with ulcerative colitis. *Clin Exp Med*. (2021) 21:379–88. doi: 10.1007/s10238-021-00702-2

70. Dayharsh GA, Loftus EVJr, Sandborn WJ, Tremaine WJ, Zinsmeister AR, Witzig TE, et al. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology*. (2002) 122:72–7. doi: 10.1053/gast.2002.30328

71. Baars JE, Markus T, Kuipers EJ, van der Woude CJ. Patients' preferences regarding shared decision-making in the treatment of inflammatory bowel disease: results from a patient-empowerment study. *Digestion*. (2010) 81:113–9. doi: 10.1159/000253862

72. Glass KE, Wills CE, Holloman C, Olson J, Hechmer C, Miller CK, et al. Shared decision making and other variables as correlates of satisfaction with health care decisions in a United States national survey. *Patient Educ Couns*. (2012) 88:100–5. doi: 10.1016/j.pec.2012.02.010

73. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care*. (2009) 47:826–34. doi: 10.1097/MLR.0b013e31819a5acc

74. Burisch J, Vegh Z, Pedersen N, Cuković-Čavka S, Turk N, Kaimakliotis I, et al. Health care and patients' education in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom study. *J Crohns Colitis*. (2014) 8:811–8. doi: 10.1016/j.crohns.2013.12.023

75. Chew D, Zhiqin W, Ibrahim N, Ali RAR. Optimizing the multidimensional aspects of the patient-physician relationship in the management of inflammatory bowel disease. *Intest Res*. (2018) 16:509–21. doi: 10.5217/ir.2018.00074

76. Drossman DA, Leserman J, Li ZM, Mitchell CM, Zagami EA, Patrick DL. The rating form of IBD patient concerns: a new measure of health status. *Psychosom Med*. (1991) 53:701–12. doi: 10.1097/00006842-199111000-00010

77. Bernstein KI, Promislow S, Carr R, Rawsthorne P, Walker JR, Bernstein CN. Information needs and preferences of recently diagnosed patients with inflammatory bowel disease. *Inflamm Bowel Dis*. (2011) 17:590–8. doi: 10.1002/ibd.21363

78. Rubin DT, Hart A, Panaccione R, Armuzzi A, Suvanto U, Deuring JJ, et al. Ulcerative colitis narrative global survey findings: communication gaps and agreements between patients and physicians. *Inflamm Bowel Dis*. (2021) 27:1096–106. doi: 10.1093/ibd/izaa257

79. Christensen B, Prentice RE, Al-Ani AH, Zhang E, Bedell A, Rubin DT. Self-reported failure to address sexual function in patients with inflammatory bowel disease by gastroenterologists: barriers and areas for improvement. *Inflamm Bowel Dis*. (2022) 28:1465–8. doi: 10.1093/ibd/izac025

80. Alexakis C, Davies G, Stephens J, Clark S, Rogers S, Poullis A. Perspectives and attitudes of young patients with inflammatory bowel disease: symptoms, burden of disease and communication with their healthcare professionals. *Frontline Gastroenterol*. (2014) 5:197–202. doi: 10.1136/flgastro-2013-100400

81. Linn AJ, Schouten BC, Sanders R, van Weert JCM, Bylund CL. Talking about Dr. Google: communication strategies used by nurse practitioners and patients with inflammatory bowel disease in the Netherlands to discuss online health information. *Patient Educ Couns*. (2020) 103:1216–22. doi: 10.1016/j.pec.2020.01.011

82. Fischhoff B, et al. Communicating Risks and Benefits: An Evidence-Based User's Guide. (2011). Available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm268078.html

83. Kurt S, Caron B, Gouynou C, Netter P, Vaizey CJ, Wexner SD, et al. Faecal incontinence in inflammatory bowel disease: the Nancy experience. *Dig Liver Dis*. (2022) 54:1195–201. doi: 10.1016/j.dld.2022.01.125

84. Marinelli C, Savarino EV, Marsilio I, Lorenzon G, Gavaruzzi T, D'Incà R, et al. Sleep disturbance in inflammatory bowel disease: prevalence and risk factors – a cross-sectional study. *Sci Rep*. (2020) 10:507. doi: 10.1038/s41598-020-57460-6

85. World Health Organization. International classification of impairments, disabilities and handicaps of the World Health Organisation. (1976). Available at: https://apps.who.int/iris/bitstream/handle/10665/41003/9241541261_eng.pdf;sequence=1

86. Tannoury J, Nachury M, Martins C, Serrero M, Filippi J, Roblin X, et al. Determinants of IBD-related disability: a cross-sectional survey from the GETAID. *Aliment Pharmacol Ther*. (2021) 53:1098–107. doi: 10.1111/apt.16353

87. Peyrin-Biroulet L, Cieza A, Sandborn WJ, Coenen M, Chowers Y, Hibi T, et al. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut*. (2012) 61:241–7. doi: 10.1136/gutjnl-2011-300049

88. Ghosh S, Louis E, Beaugerie L, Bossuyt P, Bouguen G, Bourreille A, et al. Development of the IBD disk: a visual self-administered tool for assessing disability in inflammatory bowel diseases. *Inflamm Bowel Dis*. (2017) 23:333–40. doi: 10.1097/MIB.0000000000001033

89. Marinelli C, Savarino E, Inferrera M, Lorenzon G, Rigo A, Ghisa M, et al. Influencing disability and quality of life during treatment: a cross-sectional study on IBD patients. *Gastroenterol Res Pract*. (2019) 2019:5354320. doi: 10.1155/2019/5354320

90. Shafer LA, Walker JR, Chhibba T, Targownik LE, Singh H, Ivekovic M, et al. Health care indicators of moderate to severe IBD and subsequent IBD-related disability: a longitudinal study. *Inflamm Bowel Dis*. (2019) 25:1996–2005. doi: 10.1093/ibd/izz102

91. Kayal M, Ungaro RC, Riggs A, Kamal K, Agrawal M, Cohen-Mekelburg S, et al. Ileal pouch anal anastomosis for the Management of Ulcerative Colitis is Associated with Significant Disability. *Clin Gastroenterol Hepatol*. (2022) 20:e761–9. doi: 10.1016/j.cgh.2021.05.033

92. Paulides E, Daker C, Frampton C, Gearry RB, Eglinton T, de Boer NKH, et al. Overcoming workplace disability in IBD patients: an observational study. *Inflamm Intest Dis*. (2020) 5:84–92. doi: 10.1159/000506702

93. Ramos A, Calvet X, Sicilia B, Vergara M, Figuerola A, Motos J, et al. IBD-related work disability in the community: prevalence, severity and predictive factors. A cross-sectional study. *United Eur Gastroenterol J*. (2015) 3:335–42. doi: 10.1177/2050640615577532

94. Leso V, Gervetti P, Macrini MC, Russo F, Iavicoli I. Inflammatory bowel diseases and work disability: a systematic review of predictive factors. *Eur Rev Med Pharmacol Sci*. (2021) 25:165–81. doi: 10.26355/eurrev_202101_24382

95. van Gennep S, de Boer NKH, Gielen ME, Rietdijk ST, Gecse KB, Ponsioen CY, et al. Impaired quality of working life in inflammatory bowel disease patients. *Dig Dis Sci*. (2021) 66:2916–24. doi: 10.1007/s10620-020-06647-y

96. Everhov ÅH, Bruze G, Söderling J, Askling J, Halfvarson J, Westberg K, et al. Women's earnings are more affected by inflammatory bowel disease than Men's: a register-based Swedish cohort study. *J Crohns Colitis*. (2021) 15:980–7. doi: 10.1093/ecco-jcc/jjaa238

97. Allen PB, Gower-Rousseau C, Danese S, Peyrin-Biroulet L. Preventing disability in inflammatory bowel disease. *Ther Adv Gastroenterol*. (2017) 10:865–76. doi: 10.1177/1756283X17732720

98. Cococcia S, Lenti MV, Mengoli C, Klersy C, Borrelli de Andreis F, Borrelli de Andreis F, et al. Validation of the Italian translation of the perceived stigma scale and resilience assessment in inflammatory bowel disease patients. *World J Gastroenterol*. (2021) 27:6647–58. doi: 10.3748/wjg.v27.i39.6647

99. Taft TH, Keefer L. A systematic review of disease-related stigmatization in patients living with inflammatory bowel disease. *Clin Exp Gastroenterol*. (2016) 9:49–58. doi: 10.2147/CEG.S83533

100. Taft TH, Keefer L, Leonhard C, Nealon-Woods M. Impact of perceived stigma on inflammatory bowel disease patient outcomes. *Inflamm Bowel Dis*. (2009) 15:1224–32. doi: 10.1002/ibd.20864

101. Link BG, Phelan JC. Conceptualizing stigma. *Annu Rev Sociol*. (2001) 27:363–85. doi: 10.1146/annurev.soc.27.1.363

102. Corrigan PW, Watson AC. Understanding the impact of stigma on people with mental illness. *World Psychiatry*. (2002) 1:16–20.

103. Mahajan AP, Sayles JN, Patel VA, Remien RH, Sawires SR, Ortiz DJ, et al. Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. *AIDS*. (2008) 22:S67–79. doi: 10.1097/01.aids.0000327438.13291.62

104. Lebel S, Devins GM. Stigma in cancer patients whose behavior may have contributed to their disease. *Future Oncol*. (2008) 4:717–33. doi: 10.2217/14796694.4.5.717

105. Jones MP, Keefer L, Bratten J, Taft TH, Crowell MD, Levy R, et al. Development and initial validation of a measure of perceived stigma in irritable bowel syndrome. *Psychol Health Med*. (2009) 14:367–74. doi: 10.1080/13548500902865956

106. The Road to Resilience – American Psychological Association; Available at: https://www.apa.org/ (Accessed November 10, 2022).

107. Cal SF, Sá LR, Glustak ME, Santiago MB. Resilience in chronic diseases: a systematic review. *Cogent Psychol*. (2015) 2:1024928. doi: 10.4172/2324-005.1000176

108. Quiceno JM, Venaccio S. Resilience: a perspective from the chronic disease in the adult population. *Pensam Psicol*. (2011) 9:69–82. doi: 10.1007/978-3-030-32811-5_117-1

109. Ghanei Gheshlagh R, Sayehmiri K, Ebadi A, Dalvandi A, Dalvand S, Nourozi TK. Resilience of patients with chronic physical diseases: a systematic review and meta-analysis. *Iran Red Crescent Med J*. (2016) 18:e38562. doi: 10.5812/ircmj.38562

110. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson resilience scale (CD-RISC). *Depress Anxiety*. (2003) 18:76–82. doi: 10.1002/da.10113

111. Macedo T, Wilheim L, Gonçalves R, Coutinho ES, Vilete L, Figueira I, et al. Building resilience for future adversity: a systematic review of interventions in non-clinical samples of adults. *BMC Psychiatry*. (2014) 14:227. doi: 10.1186/s12888-014-0227-6

112. Hwang JH, Yu CS. Depression and resilience in ulcerative colitis and Crohn's disease patients with ostomy. *Int Wound J*. (2019) 16:62–70. doi: 10.1111/iwj.13076

113. Fiorino G, Danese S. The new frontier: certifying quality standards in the inflammatory bowel disease care. *United European Gastroenterol J*. (2021) 9:745–7. doi: 10.1002/ueg2.12122

114. Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, et al. ECCO guidelines on the prevention, diagnosis, and Management of Infections in inflammatory bowel disease. *J Crohns Colitis*. (2021) 15:879–913. doi: 10.1093/ecco-jcc/jjab052

115. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis*. (2019) 13:144–64. doi: 10.1093/ecco-jcc/jjy113

116. Moffett P, Moore G. The standard of care: legal history and definitions: the bad and good news. *West J Emerg Med*. (2011) 12:109–12.

117. Fiorino G, Allocca M, Chaparro M, Coenen S, Fidalgo C, Younge L, et al. 'Quality of Care' standards in inflammatory bowel disease: a systematic review. *J Crohns Colitis*. (2019) 13:127–37. doi: 10.1093/ecco-jcc/jjy140

118. Fiorino G, Lytras T, Younge L, Fidalgo C, Coenen S, Chaparro M, et al. Quality of care standards in inflammatory bowel diseases: a European Crohn's and colitis organisation [ECCO] position paper. *J Crohns Colitis*. (2020) 14:1037–48. doi: 10.1093/ecco-jcc/jjaa023

119. E.C.C.O. (ECCO), E-QUALITY: ECCO QUALITY OF CARE PROJECT, (2021). Available at: https://www.ecco-ibd.eu/education/e-quality.html (Accessed April 27, 2022).

120. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. (2009) 361:2066–78. doi: 10.1056/NEJMra0804647

121. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. (2012) 142:1102–1111.e2. doi: 10.1053/j.gastro.2012.01.035

122. Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc*. (2006) 63:433–42. doi: 10.1016/j.gie.2005.08.011

123. Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther*. (2016) 43:317–33. doi: 10.1111/apt.13475

124. André C, Descos L, Vignal J, Gillon J. C-reactive protein as a predictor of relapse in asymptomatic patients with Crohn's disease. *Scott Med J*. (1983) 28:26–9. doi: 10.1177/003693308302800106

125. Abraham BP, Kane S. Fecal markers: calprotectin and lactoferrin. *Gastroenterol Clin N Am*. (2012) 41:483–95. doi: 10.1016/j.gtc.2012.01.007

126. Lin JF, Chen JM, Zuo JH, Yu A, Xiao ZJ, Deng FH, et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis*. (2014) 20:1407–15. doi: 10.1097/MIB.0000000000000057

127. Buisson A, Mak WY, Andersen MJ, Lei D, Kahn SA, Pekow J, et al. Faecal calprotectin is a very reliable tool to predict and monitor the risk of relapse after therapeutic De-escalation in patients with inflammatory bowel diseases. *J Crohns Colitis*. (2019) 13:1012–24. doi: 10.1093/ecco-jcc/jjz023

128. Ferreiro-Iglesias R, Barreiro-de Acosta M, Lorenzo-Gonzalez A, Dominguez-Muñoz JE. Accuracy of consecutive fecal calprotectin measurements to predict relapse in inflammatory bowel disease patients under maintenance with anti-TNF therapy: a prospective longitudinal cohort study. *J Clin Gastroenterol*. (2018) 52:229–34. doi: 10.1097/MCG.0000000000000774

129. Kittanakom S, Shajib MS, Garvie K, Turner J, Brooks D, Odeh S, et al. Comparison of fecal calprotectin methods for predicting relapse of pediatric inflammatory bowel disease. *Can J Gastroenterol Hepatol*. (2017) 2017:1450970. doi: 10.1155/2017/1450970

130. Diederen K, Hoekman DR, Leek A, Wolters VM, Hummel TZ, de Meij TG, et al. Raised faecal calprotectin is associated with subsequent symptomatic relapse, in children and adolescents with inflammatory bowel disease in clinical remission. *Aliment Pharmacol Ther*. (2017) 45:951–60. doi: 10.1111/apt.13950

131. Roblin X, Duru G, Williet N, Del Tedesco E, Cuilleron M, Jarlot C, et al. Development and internal validation of a model using fecal calprotectin in combination with infliximab trough levels to predict clinical relapse in Crohn's disease. *Inflamm Bowel Dis*. (2017) 23:126–32. doi: 10.1097/MIB.0000000000000986

132. Naismith GD, Smith LA, Barry SJ, Munro JI, Laird S, Rankin K, et al. A prospective evaluation of the predictive value of faecal calprotectin in quiescent Crohn's disease. *J Crohns Colitis.* (2014) 8:1022–9. doi: 10.1016/j.crohns.2014.01.029

133. Laharie D, Mesli S, El Hajbi F, Chabrun E, Chanteloup E, Capdepont M, et al. Prediction of Crohn's disease relapse with faecal calprotectin in infliximab responders: a prospective study. *Aliment Pharmacol Ther.* (2011) 34:462–9. doi: 10.1111/j.1365-2036.2011.04743.x

134. D'Incà R, Dal Pont E, Di Leo V, Benazzato L, Martinato M, Lamboglia F, et al. Can calprotectin predict relapse risk in inflammatory bowel disease? *Am J Gastroenterol.* (2008) 103:2007–14. doi: 10.1111/j.1572-0241.2008.01870.x

135. Costa F, Mumolo MG, Ceccarelli L, Bellini M, Romano MR, Sterpi C, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut.* (2005) 54:364–8. doi: 10.1136/gut.2004.043406

136. Tibble JA, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology.* (2000) 119:15–22. doi: 10.1053/gast.2000.8523

137. Mao R, Xiao YL, Gao X, Chen BL, He Y, Yang L, et al. Faecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. *Inflamm Bowel Dis.* (2012) 18:1894–9. doi: 10.1002/ibd.22861

138. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology.* (2015) 148:938–947.e1. doi: 10.1053/j.gastro.2015.01.026

139. Tham YS, Yung DE, Fay S, Yamamoto T, Ben-Horin S, Eliakim R, et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. *Ther Adv Gastroenterol.* (2018) 11:1756284818785571. doi: 10.1177/1756284818785571

140. Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology.* (2021) 161:47–65. doi: 10.1053/j.gastro.2021.04.063

141. Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* (2016) 10:CD000545. doi: 10.1002/14651858.CD000545.pub5

142. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev.* (2015) 2016:CD000067. doi: 10.1002/14651858.CD000067.pub3

143. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi PG. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut.* (2006) 55:47–53. doi: 10.1136/gut.2005.068809

144. Ferretti F, Cannatelli R, Monico MC, Maconi G, Ardizzone S. An update on current Pharmacotherapeutic options for the treatment of ulcerative colitis. *J Clin Med.* (2022) 11:2302. doi: 10.3390/jcm11092302

145. Hanauer SB, Sandborn WJ, Lichtenstein GR. Evolving considerations for Thiopurine therapy for inflammatory bowel diseases-A clinical practice update: commentary. *Gastroenterology.* (2019) 156:36–42. doi: 10.1053/j.gastro.2018.08.043

146. Jharap B, Seinen ML, de Boer NK, van Ginkel JR, Linskens RK, Kneppelhout JC. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. *Inflamm Bowel Dis.* (2010) 16:1541–9. doi: 10.1002/ibd.21221

147. Luber RP, Honap S, Cunningham G, Irving PM. Can we predict the toxicity and response to thiopurines in iunfalmmatory bowel disease? *Front Med.* (2019) 6:279. doi: 10.3389/fmed.2019.00279

148. Chaparro M, Ordás I, Cabré E, Garcia-Sanchez V, Bastida G, Peñalva M, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. *Inflamm Bowel Dis.* (2013) 19:1404–10. doi: 10.1097/MIB.0b013e318281f28f

149. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol.* (2011) 106:674–84. doi: 10.1038/ajg.2011.60

150. Papamichael K, Gils A, Rutgeerts P, Levesque BG, Vermeire S, Sandborn WJ, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis.* (2015) 21:182–97. doi: 10.1097/MIB.0000000000000202

151. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* (2013) 369:699–710. doi: 10.1056/NEJMoa1215734

152. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* (2013) 369:711–21. doi: 10.1056/NEJMoa1215739

153. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JRP, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* (2016) 375:1946–60. doi: 10.1056/NEJMoa1602773

154. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* (2019) 381:1201–14. doi: 10.1056/NEJMoa1900750

155. Gisbert JP, Chaparro M. Predictors of primary response to biologic treatment [anti-TNF, Vedolizumab, and Ustekinumab] in patients with inflammatory bowel disease: from basic science to clinical practice. *J Crohns Colitis.* (2020) 14:694–14709. doi: 10.1093/ecco-jcc/jjz195

156. Inamdar S, Volfson A, Rosen L, Sunday S, Katz S, Sultan K. Smoking and early infliximab response in Crohn's disease: a meta-analysis. *J Crohns Colitis.* (2015) 9:140–9146. doi: 10.1093/ecco-jcc/jju018

157. Narula N, Fedorak RN. Does smoking reduce infliximab's effectiveness against Crohn's disease? *Can J Gastroenterol.* (2009) 23:121–5. doi: 10.1155/2009/431349

158. Beltrán B, Iborra M, Sáez-González E, Marqués-Miñana MR, Moret I, Cerrillo E, et al. Fecal calprotectin pretreatment and induction infliximab levels for prediction of primary nonresponse to infliximab therapy in Crohn's disease. *Dig Dis.* (2019) 37:108–15. doi: 10.1159/000492626

159. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* (2010) 362:1383–95. doi: 10.1056/NEJMoa0904492

160. Ho GT, Lee HM, Brydon G, Ting T, Hare N, Drummond H, et al. Fecal calprotectin predicts the clinical course of acute severe ulcerative colitis. *Am J Gastroenterol.* (2009) 104:673–8. doi: 10.1038/ajg.2008.119

161. Jürgens M, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. *Clin Gastroenterol Hepatol.* (2011) 9:421–7.e1. doi: 10.1016/j.cgh.2011.02.008

162. Louis E, Vermeire S, Rutgeerts P, De Vos M, Van Gossum A, Pescatore P, et al. A positive response to infliximab in Crohn disease: association with a higher systemic inflammation before treatment but not with −308 TNF gene polymorphism. *Scand J Gastroenterol.* (2002) 37:818–24. doi: 10.1080/gas.37.7.818.824

163. Angelison L, Almer S, Eriksson A, Karling P, Fagerberg U, Halfvarson J, et al. Swedish Organization for the Study of inflammatory bowel diseases (SOIBD). Long-term outcome of infliximab treatment in chronic active ulcerative colitis: a Swedish multicentre study of 250 patients. *Aliment Pharmacol Ther.* (2017) 45:519–32. doi: 10.1111/apt.13893

164. Beswick L, Rosella O, Rosella G, Headon B, Sparrow MP, Gibson PR, et al. Exploration of predictive biomarkers of early infliximab response in acute severe colitis: a prospective pilot study. *J Crohns Colitis.* (2018) 12:289–97. doi: 10.1093/ecco-jcc/jjx146

165. Dahlén R, Magnusson MK, Bajor A, Lasson A, Ung KA, Strid H, et al. Global mucosal and serum cytokine profile in patients with ulcerative colitis undergoing anti-TNF therapy. *Scand J Gastroenterol.* (2015) 50:1118–26. doi: 10.3109/00365521.2015.1031167

166. Louis E, El Ghoul Z, Vermeire S, Dall'Ozzo S, Rutgeerts P, Paintaud G, et al. Association between polymorphism in IgG fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther.* (2004) 19:511–9. doi: 10.1111/j.1365-2036.2004.01871.x

167. Sazonovs A, Kennedy NA, Moutsianas L, Heap GA, Rice DL, Reppell M, et al. PANTS consortium. HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology.* (2020) 158:189–99. doi: 10.1053/j.gastro.2019.09.041

168. A SPECIAL MEETING REVIEW EDITION: Highlights in anti-tumor necrosis factor monitoring and antibody monitoring from the 2014 DDW meeting: digestive disease week 2014 may 3-6, 2014 • Chicago, Illinois. *Gastroenterol Hepatol (N Y).* (2014) 10:1–20.

169. Gonczi L, Vegh Z, Golovics PA, Rutka M, Gecse KB, Bor R, et al. Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels and antidrug antibody levels or clinical and biochemical markers play the more important role? *J Crohns Colitis.* (2017) 11:jjw203–705. doi: 10.1093/ecco-jcc/jjw203

170. Borren NZ, Paulides E, Frinack JL, Olson RN, Willrich MAV, van der Woude CJ, et al. Infliximab trough levels are not predictive of relapse in patients with IBD in endoscopic remission: a multicenter cohort study. *Dig Dis Sci.* (2021) 66:3548–54. doi: 10.1007/s10620-020-06645-0

171. Gaujoux R, Starosvetsky E, Maimon N, Vallania F, Bar-Yoseph H, Pressman S, et al. Cell-centred meta-analysis reveals baseline predictors of anti-TNFα non-response in biopsy and blood of patients with IBD. *Gut.* (2019) 68:604–14. doi: 10.1136/gutjnl-2017-315494

172. Verstockt B, Verstockt S, Dehairs J, Ballet V, Blevi H, Wollants WJ, et al. Low TREM1 expression in whole blood predicts anti-TNF response in inflammatory bowel disease. *EBioMedicine.* (2019) 40:733–42. doi: 10.1016/j.ebiom.2019.01.027

173. Bertani L, Fornai M, Fornili M, Antonioli L, Benvenuti L, Tapete G, et al. Serum oncostatin M at baseline predicts mucosal healing in Crohn's disease patients treated with infliximab. *Aliment Pharmacol Ther.* (2020) 52:284–91. doi: 10.1111/apt.15870

174. Minar P, Lehn C, Tsai YT, Jackson K, Rosen MJ, Denson LA. Elevated pretreatment plasma Oncostatin M is associated with poor biochemical response to infliximab. *Crohns Colitis.* (2019) 1:otz026. doi: 10.1093/crocol/otz026

175. Atreya R, Neumann H, Neufert C, Waldner MJ, Billmeier U, Zopf Y, et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. *Nat Med.* (2014) 20:313–8. doi: 10.1038/nm.3462

176. Rath T, Bojarski C, Neurath MF, Atreya R. Molecular imaging of mucosal alpha4beta7 integrin expression with the fluorescent anti-adhesion antibody vedolizumab in Crohn's disease. *Gastrointest Endosc*. (2017) 86:406–8. doi: 10.1016/j.gie.2017.01.012

177. Iacucci M, Jeffery L, Acharjee A, Grisan E, Buda A, Nardone OM, et al. Computer-aided imaging analysis of probe-based confocal laser Endomicroscopy with molecular labeling and gene expression identifies markers of response to biological therapy in IBD patients: the Endo-omics study. *Inflamm Bowel Dis*. (2022):izac233. doi: 10.1093/ibd/izac233

178. Ananthakrishnan AN, Luo C, Yajnik V, Khalili H, Garber JJ, Stevens BW, et al. Gut microbiome function predicts response to anti-integrin biologic therapy in inflammatory bowel diseases. *Cell Host Microbe*. (2017) 21:603–610.e3. doi: 10.1016/j.chom.2017.04.010

179. Limdi JK, Farraye FA. Real-time use of artificial intelligence at colonoscopy predicts relapse in ulcerative colitis: predicting with "intelligence". *Gastrointest Endosc*. (2022) 95:757–9. doi: 10.1016/j.gie.2021.12.048

180. Tontini GE, Rimondi A, Vernero M, Neumann H, Vecchi M, Bezzio C, et al. Artificial intelligence in gastrointestinal endoscopy for inflammatory bowel disease: a systematic review and new horizons. *Ther Adv Gastroenterol*. (2021) 14:17562848211017730. doi: 10.1177/17562848211017730

181. Iacucci M, Smith SCL, Bazarova A, Shivaji UN, Bhandari P, Cannatelli R, et al. An international multicenter real-life prospective study of electronic Chromoendoscopy score PICaSSO in ulcerative colitis. *Gastroenterology*. (2021) 160:1558–1569.e8. doi: 10.1053/j.gastro.2020.12.024

182. Nardone OM, Bazarova A, Bhandari P, Cannatelli R, Daperno M, Ferraz J, et al. PICaSSO virtual electronic chromoendoscopy accurately reflects combined endoscopic and histological assessment for prediction of clinical outcomes in ulcerative colitis. United European. *Gastroenterol J*. (2022) 10:147–59. doi: 10.1002/ueg2.12185

183. Iacucci M, Cannatelli R, Parigi TL, Buda A, Labarile N, Nardone OM. OP16 the first virtual chromoendoscopy artificial intelligence system to detect endoscopic and histologic remission in ulcerative colitis. *J Crohn's Colitis*. (2022) 16:i017–8. doi: 10.1093/ecco-jcc/jjab232.015

184. Villanacci V, Parigi TL, Del Amor R, Mesguer Esbrì P, Gui X, Bazarova A, et al. OP15 A new simplified histology artificial intelligence system for accurate assessment of remission in ulcerative colitis. *J Crohn's Colitis*. (2022) 16:i015–7. doi: 10.1093/ecco-jcc/jjab232.014

185. Bossuyt P, Nakase H, Vermeire S, de Hertogh G, Eelbode T, Ferrante M, et al. Automatic, computer-aided determination of endoscopic and histological inflammation in patients with mild to moderate ulcerative colitis based on red density. *Gut*. (2020) 69:1778–86. doi: 10.1136/gutjnl-2019-320056

186. Bossuyt P, De Hertogh G, Eelbode T, Vermeire S, Bisschops R. Computer-aided diagnosis with monochromatic light endoscopy for scoring histologic remission in ulcerative colitis. *Gastroenterology*. (2021) 160:23–5. doi: 10.1053/j.gastro.2020.09.053

187. Stidham RW, Liu W, Bishu S, Rice MD, Higgins PDR, Zhu J, et al. Performance of a deep learning model vs human reviewers in grading endoscopic disease severity of patients with ulcerative colitis. *JAMA Netw Open*. (2019) 2:e193963. doi: 10.1001/jamanetworkopen.2019.3963

188. Gottlieb K, Requa J, Karnes W, Chandra Gudivada R, Shen J, Rael E, et al. Central Reading of ulcerative colitis clinical trial videos using neural networks. *Gastroenterology*. (2021) 160:710–719.e2. doi: 10.1053/j.gastro.2020.10.024

189. Yao H, Stidham RW, Soroushmehr R, Gryak J, Najarian K. Automated detection of non-informative frames for colonoscopy through a combination of deep learning and feature extraction. *Annu Int Conf IEEE Eng Med Biol Soc*. (2019) 2019:2402–6. doi: 10.1109/EMBC.2019.8856625

190. Takenaka K, Ohtsuka K, Fujii T, Oshima S, Okamoto R, Watanabe M. Deep neural network accurately predicts prognosis of ulcerative colitis using endoscopic images. *Gastroenterology*. (2021) 160:2175–2177.e3. doi: 10.1053/j.gastro.2021.01.210

191. Kabir M, Fofaria R, Arebi N, Bassett P, Tozer PJ, Hart AL, et al. Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present). *Aliment Pharmacol Ther*. (2020) 52:5–19. doi: 10.1111/apt.15778

192. Iacucci M, Cannatelli R, Tontini GE, Panaccione R, Danese S, et al. Improving the quality of surveillance colonoscopy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol*. (2019) 4:971–83. doi: 10.1016/S2468-1253(19)30194-3

193. Maeda Y, Kudo SE, Ogata N, Kuroki T, Takashina Y, Takishima K, et al. Use of advanced endoscopic technology for optical characterization of neoplasia in patients with ulcerative colitis: a systematic review. *Dig Endosc*. (2022) 34:1297–310. doi: 10.1111/den.14335

194. Murthy SK, Feuerstein JD, Nguyen GC, Velayos FS. AGA clinical practice update on endoscopic surveillance and Management of Colorectal Dysplasia in inflammatory bowel diseases: expert review. *Gastroenterology*. (2021) 161:1043–1051.e4. doi: 10.1053/j.gastro.2021.05.063

195. Maeda Y, Kudo SE, Ogata N, Misawa M, Mori Y, Mori K, et al. Can artificial intelligence help to detect dysplasia in patients with ulcerative colitis? *Endoscopy*. (2021) 53:E273–4. doi: 10.1055/a-1261-2944

196. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. (2014) 8:443–68. doi: 10.1016/j.crohns.2013.12.013

197. Mazzola G, Macaluso FS, Adamoli L, Renna S, Cascio A, Orlando A. Diagnostic and vaccine strategies to prevent infections in patients with inflammatory bowel disease. *J Infect*. (2017) 74:433–41. doi: 10.1016/j.jinf.2017.02.009

198. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. (2013) 58:e44–e100. doi: 10.1093/cid/cit684

199. Cottone M, Kohn A, Daperno M, Armuzzi A, Guidi L, D'Inca R, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol*. (2011) 9:30–5. doi: 10.1016/j.cgh.2010.09.026

200. Toruner M, Loftus EVJr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. (2008) 134:929–36. doi: 10.1053/j.gastro.2008.01.012

201. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. (2012) 107:1409–22. doi: 10.1038/ajg.2012.218

202. Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. (2017) 66:839–51. doi: 10.1136/gutjnl-2015-311079

203. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. (2016) 2016:CD007572. doi: 10.1002/14651858.CD007572.pub3

204. Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. Herpes zoster infection in patients with ulcerative colitis receiving Tofacitinib. *Inflamm Bowel Dis*. (2018) 24:2258–65. doi: 10.1093/ibd/izy131

205. Guillo L, Rabaud C, Choy EH, D'Amico F, Danese S, Ng SC, et al. Herpes zoster and vaccination strategies in inflammatory bowel diseases: a practical guide. *Clin Gastroenterol Hepatol*. (2022) 20:481–90. doi: 10.1016/j.cgh.2020.10.027

206. European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. (2012) 57:167–85. doi: 10.1016/j.jhep.2012.02.010

207. Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for active tuberculosis in inflammatory bowel disease patients. *Clin Gastroenterol Hepatol*. (2007) 5:1070–1075.e1. doi: 10.1016/j.cgh.2007.04.007

208. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. (2009) 374:1617–25. doi: 10.1016/S0140-6736(09)61302-7

209. Sokol H, Beaugerie L, Maynadié M, Laharie D, Dupas JL, Flourié B, et al. Excess primary intestinal lymphoproliferative disorders in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. (2012) 18:2063–71. doi: 10.1002/ibd.22889

210. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal pap smears in women with inflammatory bowel disease. *Am J Gastroenterol*. (2008) 103:631–6. doi: 10.1111/j.1572-0241.2007.01582.x

211. Harrison LH. Epidemiological profile of meningococcal disease in the United States. *Clin Infect Dis*. (2010) 50:S37–44. doi: 10.1086/648963

212. Cohn AC, MacNeil JR, Clark TA, Ortega-Sanchez IR, Briere EZ, Meissner HC, et al. Prevention and control of meningococcal disease: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. (2013) 22:1–28.

213. De León-Rendón JL, Hurtado-Salazar C, Yamamoto-Furusho JK. Aspects of inflammatory bowel disease during the COVID-19 pandemic and general considerations. *Rev Gastroenterol Mex (Engl Ed)*. (2020) 85:295–302. doi: 10.1016/j.rgmx.2020.05.001

214. Siegel CA, Melmed GY, McGovern DP, Rai V, Krammer F, Rubin DT, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut*. (2021) 70:635–40. doi: 10.1136/gutjnl-2020-324000

215. Macaluso FS, Liguori G, Galli M. Vaccinations in patients with inflammatory bowel disease. *Dig Liver Dis*. (2021) 53:1539–45. doi: 10.1016/j.dld.2021.05.015

216. Frontali A, Cohen L, Bridoux V, Myrelid P, Sica G, Poggioli G, et al. Segmental colectomy for ulcerative colitis: is there a place in selected patients without active colitis? An international multicentric retrospective study in 72 patients. *J Crohns Colitis*. (2020) 14:1687–92. doi: 10.1093/ecco-jcc/jjaa107

217. Øresland T, Bemelman WA, Sampietro GM, Spinelli A, Windsor A, Ferrante M, et al. European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis*. (2015) 9:4–25. doi: 10.1016/j.crohns.2014.08.012

218. Pellino G, Keller DS, Sampietro GM, Carvello M, Celentano V, Coco C, et al. Inflammatory bowel disease position statement of the Italian Society of Colorectal Surgery (SICCR): ulcerative colitis. *Tech Coloproctol*. (2020) 24:397–419. doi: 10.1007/s10151-020-02175-z

219. Colombo F, Sahami S, De Buck Van Overstraeten A, Tulchinsky H, Mege D, Dotan I, et al. Restorative Proctocolectomy in elderly IBD patients: a multicentre comparative study on safety and efficacy. *J Crohns Colitis*. (2017) 11:671–9. doi: 10.1093/ecco-jcc/jjw209

220. Sampietro GM, Colombo F, Corsi F. Sequential approach for a critical-view COlectomy (SACCO): a laparoscopic technique to reduce operative time and complications in IBD acute severe colitis. *J Clin Med*. (2020) 9:3382. doi: 10.3390/jcm9103382

221. Frontali A, Colombo F, Sampietro GM. Acute severe ulcerative colitis: how to reduce operating time under 150 min for emergency laparoscopic colectomy – a video vignette. *Color Dis*. (2021) 23:3280–1. doi: 10.1111/codi.15928

222. Bartels SA, Dhoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg*. (2012) 256:1045–8. doi: 10.1097/SLA.0b013e318250caa9

223. Bemelman WA, Warusavitarne J, Sampietro GM, Serclova Z, Zmora O, Luglio G, et al. ECCO-ESCP consensus on surgery for Crohn's disease. *J Crohns Colitis*. (2018) 12:1–16. doi: 10.1093/ecco-jcc/jjx061

224. Cristaldi M, Sampietro GM, Danelli PG, Bollani S, Bianchi Porro G, Taschieri AM. Long-term results and multivariate analysis of prognostic factors in 138 consecutive patients operated on for Crohn's disease using "bowel-sparing" techniques. *Am J Surg*. (2000) 179:266–70. doi: 10.1016/s0002-9610(00)00334-2

225. Parente F, Sampietro GM, Molteni M, Greco S, Anderloni A, Sposito C, et al. Behaviour of the bowel wall during the first year after surgery is a strong predictor of symptomatic recurrence of Crohn's disease: a prospective study. *Aliment Pharmacol Ther*. (2004) 20:959–68. doi: 10.1111/j.1365-2036.2004.02245.x

226. Sampietro GM, Cristaldi M, Maconi G, Parente F, Sartani A, Ardizzone S, et al. A prospective, longitudinal study of nonconventional strictureplasty in Crohn's disease. *J Am Coll Surg*. (2004) 199:8–20. doi: 10.1016/j.jamcollsurg.2004.01.039

227. Maconi G, Colombo E, Sampietro GM, Lamboglia F, D'Incà R, Daperno M. CARD15 gene variants and risk of reoperation in Crohn's disease patients. *Am J Gastroenterol*. (2009) 104:2483–91. doi: 10.1038/ajg.2009.413

228. Sampietro GM, Corsi F, Maconi G, Ardizzone S, Frontali A, Corona A, et al. Prospective study of long-term results and prognostic factors after conservative surgery for small bowel Crohn's disease. *Clin Gastroenterol Hepatol*. (2009) 7:183–91. doi: 10.1016/j.cgh.2008.10.008

229. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. (1990) 99:956–63. doi: 10.1016/0016-5085(90)90613-6

230. Kono T, Nomura M, Kasai S, Kohgo Y. Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol*. (2001) 96:793–7. doi: 10.1111/j.1572-0241.2001.03624.x

231. Luglio G, Rispo A, Imperatore N, Giglio MC, Amendola A, Tropeano FP, et al. Surgical prevention of anastomotic recurrence by excluding mesentery in Crohn's disease: the SuPREMe-CD study – A randomized clinical trial. *Ann Surg*. (2020) 272:210–7. doi: 10.1097/SLA.0000000000003821

232. Sampietro GM, Maconi G, Colombo F, Dilillo D, Fiorina P, D'Addio F, et al. Prevalence and significance of mesentery thickening and lymph nodes enlargement in Crohn's disease. *Dig Liver Dis*. (2022) 54:490–9. doi: 10.1016/j.dld.2021.06.030

233. Mineccia M, Maconi G, Daperno M, Cigognini M, Cherubini V, Colombo F, et al. Has the removing of the mesentery during Ileo-colic resection an impact on post-operative complications and recurrence in Crohn's disease? Results from the resection of the mesentery study (remedy). *J Clin Med*. (2022) 11:1961. doi: 10.3390/jcm11071961

234. Coffey CJ, Kiernan MG, Saheballly SM, Jarrar A, Burke JP, Kiely PA, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis*. (2018) 12:1139–50. doi: 10.1093/ecco-jcc/jjx187

235. Plevris N, Lees CW. Disease monitoring in inflammatory bowel disease: evolving principles and possibilities. *Gastroenterology*. (2022) 162:1456–1475.e1. doi: 10.1053/j.gastro.2022.01.024

236. D'Haens G, Kelly O, Battat R, Silverberg MS, Laharie D, Louis E, et al. Development and validation of a test to monitor endoscopic activity in patients with Crohn's disease based on serum levels of proteins. *Gastroenterology*. (2020) 158:515–526.e10. doi: 10.1053/j.gastro.2019.10.034

237. Facchin S, Buda A, Cardin R, Agbariah N, Zingone F, de Bona M, et al. Rapid point-of-care anti-infliximab antibodies detection in clinical practice: comparison with ELISA and potential for improving therapeutic drug monitoring in IBD patients. *Ther Adv Gastroenterol*. (2021) 14:1756284821999902. doi: 10.1177/1756284821999902

238. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. (2022) 7:161–70. doi: 10.1016/S2468-1253(21)00377-0

239. Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, et al. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. (2021) 6:1002–14. doi: 10.1016/S2468-1253(21)00312-5

240. Ben-Horin S, Novack L, Mao R, Guo J, Zhao Y, Sergienko R, et al. Efficacy of biologic drugs in short-duration versus Long-duration inflammatory bowel disease: a systematic review and an individual-patient data meta-analysis of randomized controlled trials. *Gastroenterology*. (2022) 162:482–94. doi: 10.1053/j.gastro.2021.10.037

241. Torres J, Caprioli F, Katsanos KH, Lobatón T, Micic D, Zerôncio M, et al. Predicting outcomes to optimize disease Management in Inflammatory Bowel Diseases. *J Crohns Colitis*. (2016) 10:1385–94. doi: 10.1093/ecco-jcc/jjw116

242. Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. (2017) 45:3–13. doi: 10.1111/apt.13847

243. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. (2021) 6:359–70. doi: 10.1016/S2468-1253(21)00014-5

244. Marinelli C, Zingone F, Inferrera M, Lorenzon G, Rigo A, Facchin S, et al. Factors associated with disability in patients with ulcerative colitis: a cross-sectional study. *J Dig Dis*. (2020) 21:81–7. doi: 10.1111/1751-2980.12837

245. Verstockt B, Parkes M, Lee JC. How do we predict a Patient's disease course and whether they will respond to specific treatments? *Gastroenterology*. (2022) 162:1383–95. doi: 10.1053/j.gastro.2021.12.245

246. Verstockt B, Noor NM, Marigorta UM, Pavlidis P, Deepak P, Ungaro RC. Scientific workshop steering committee. Results of the seventh scientific workshop of ECCO: precision medicine in IBD-disease outcome and response to therapy. *J Crohns Colitis*. (2021) 15:1431–42. doi: 10.1093/ecco-jcc/jjab050

247. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Belgian inflammatory bowel disease research group; North-Holland gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. (2008) 371:660–7. doi: 10.1016/S0140-6736(08)60304-9

248. Hamdeh S, Aziz M, Altayar O, Olyaee M, Murad MH, Hanauer SB. Early vs late use of anti-TNFa therapy in adult patients with Crohn disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. (2020) 26:1808–18. doi: 10.1093/ibd/izaa031

249. Bodini G, Giannini EG, De Maria C, Dulbecco P, Furnari M, Marabotto E, et al. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lémann index. *Dig Liver Dis*. (2017) 49:175–80. doi: 10.1016/j.dld.2016.10.014

250. Singh S, Stitt LW, Zou G, Khanna R, Dulai PS, Sandborn WJ, et al. Early combined immunosuppression may be effective and safe in older patients with Crohn's disease: post hoc analysis of REACT. *Aliment Pharmacol Ther*. (2019) 49:1188–94. doi: 10.1111/apt.15214

251. Raine T, Danese S. Breaking through the therapeutic ceiling: what will it take? *Gastroenterology*. (2022) 162:1507–11. doi: 10.1053/j.gastro.2021.09.078

252. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. (2017) 390:2779–89. doi: 10.1016/S0140-6736(17)32641-7

253. Irving PM, Sands BE, Hoops T, Izanec JL, Gao LL, Gasink C, et al. OP02 Ustekinumab versus adalimumab for induction and maintenance therapy in moderate-to-severe Crohn's disease: the SEAVUE study. *J Crohn's Colitis*. (2021) 15:S001–2. doi: 10.1093/ecco-jcc/jjab075.001

254. Sands BE, Peyrin-Biroulet L, Loftus EVJr, Danese S, Colombel JF, Törüner M, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. *N Engl J Med*. (2019) 381:1215–26. doi: 10.1056/NEJMoa1905725

255. Ahmed W, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, et al. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2022) 20:e361–79. doi: 10.1016/j.cgh.2021.03.034

256. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. *Inflamm Bowel Dis*. (2014) 20:2022–8. doi: 10.1097/MIB.0000000000000148

257. Barberio B, Black CJ, Savarino EV, Ford AC. Ciclosporin or infliximab as rescue therapy in acute Glucorticosteroid-refractory ulcerative colitis: systematic review and network meta-analysis. *J Crohns Colitis*. (2021) 15:733–41. doi: 10.1093/ecco-jcc/jjaa226

258. Pineton de Chambrun G, Amiot A, Bouguen G, Viennot S, Altwegg R, Louis E, et al. PROTECT-GETAID study group. Efficacy of tumor necrosis factor antagonist treatment in patients with refractory ulcerative Proctitis. *Clin Gastroenterol Hepatol*. (2020) 18:620–627.e1. doi: 10.1016/j.cgh.2019.05.060

259. Beelen EMJ, Nieboer D, Arkenbosch JHC, Regueiro MD, Satsangi J, Ardizzone S, et al. Risk prediction and comparative efficacy of anti-TNF vs Thiopurines, for preventing postoperative recurrence in Crohn's disease: a pooled analysis of 6 trials. *Clin Gastroenterol Hepatol*. (2021) 20:2741–2752.e6. doi: 10.1016/j.cgh.2021.10.021

260. Ananthakrishnan AN, Donaldson T, Lasch K, Yajnik V. Management of Inflammatory Bowel Disease in the elderly patient: challenges and opportunities. *Inflamm Bowel Dis*. (2017) 23:882–93. doi: 10.1097/MIB.0000000000001099

261. Revés J, Ungaro RC, Torres J. Unmet needs in inflammatory bowel disease. *Curr Res Pharmacol Drug Discov*. (2021) 2:100070. doi: 10.1016/j.crphar.2021.100070

262. Bzdok D, Altman N, Krzywinski M. Statistics versus machine learning. *Nat Methods*. (2018) 15:233–4. doi: 10.1038/nmeth.4642

263. Le Berre C, Sandborn WJ, Aridhi S, Devignes MD, Fournier L, Smaïl-Tabbone M, et al. Application of artificial intelligence to gastroenterology and hepatology. *Gastroenterology*. (2020) 158:76–94.e2. doi: 10.1053/j.gastro.2019.08.058

264. Chen D, Fulmer C, Gordon IO, Syed S, Stidham RW, Vande Casteele N, et al. Application of artificial intelligence to clinical practice in inflammatory bowel disease – what the clinician needs to know. *J Crohns Colitis*. (2022) 16:460–71. doi: 10.1093/ecco-jcc/jjab169