What changes in inflammatory bowel disease management can be implemented today?

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Abstract
Innovative ideas are required to improve the management of inflammatory bowel disease and to share best practice that can be implemented into clinical practice today. The use of biomarkers such as calprotectin to monitor disease progression and treatment response could help to improve management of inflammatory bowel disease, but several strategies need to be implemented to make this a reality in clinical practice. The use of calprotectin as a biomarker and the manipulation of the thiopurine pathway to extend the use of current therapies are examples of how basic research can translate into patient benefit. Translational research into the use of microbiota and predictive factors for response and toxicity to drugs, may provide future clinical applications. Global improvement in care in inflammatory bowel disease could also be advanced by improving service provision. For example, the establishment of ‘Centres of Excellence’, a global interactive inflammatory disease map, and the alignment of processes and standards of care within treatment centres may help to achieve better outcomes for patients with inflammatory bowel disease. Realization of this goal, as well as a better understanding of the aetiology of the disease, may be furthered by collaborative efforts between organizations involved in inflammatory bowel disease as well as wider collaboration across countries and globally.

1. Introduction
Inflammatory bowel disease (IBD) results in a substantial burden to individuals and society, not only because of direct and indirect medical costs, but also by causing disability. The reduction in working capacity, especially in a young and active segment of the population (described by Hommes et al. in this supplement), is the major economic and social burden of disease that outweighs the cost of drug therapy. Despite recent advances in the treatment of IBD, much remains to be done in order to improve outcomes and this has been reflected by a shift in treatment goals from improved symptoms to sustained deep remission and improved quality of life (QoL). While current research may provide innovations that will help to achieve these targets, people living with IBD require solutions today to manage their symptoms and maintain a good QoL.

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Abbreviations: CD, Crohn’s disease; CDAI, Crohn’s disease activity index; CDEIS, Crohn’s disease endoscopic index of severity; CRP, C-reactive protein; IBD, inflammatory bowel disease; QoL, quality of life; TNF, tumour necrosis factor; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.
Several different strategies are available to clinicians to help improve outcomes in IBD, but the level and delivery of care may vary across different settings. In this paper we propose innovative ideas to improve disease management both at the individual level, and from wider societal and global perspectives. Potential practical applications of research outputs in clinical practice are explored, strategies to improve standards of care in different clinical settings are proposed, and collaborative efforts to share best practice and improve knowledge about IBD are detailed.

2. Evolution of patient care
The evolution of treatment goals in IBD (see Hommes et al. in this supplement) is potentially changing the course of the disease, as well as the expectations of patients, healthcare professionals and health plan providers. Twenty years ago treatment was based on symptoms, and there was a nihilistic view, based on early studies, on the ability to achieve long-term maintenance of remission for Crohn’s disease (CD). We now recognize, however, that induction of remission and its subsequent maintenance is the standard of care. The provision of personalized medicine through, for example, a better understanding of pharmacogenetics (thiopurines) and therapeutic drug monitoring (biologics) is now becoming possible. In the future, care will be increasingly determined and optimized according to ‘biotypes’ based on genetics, serology, proteomics, metabolomics and individual microbiome patterns. In addition, treatment goals have evolved towards mucosal healing, with establishing and maintaining ‘deep remission’. It is hoped that achieving these goals will lead to improved clinical outcomes, including QoL and reduced disease-related complications, as well as pharmacoeconomic outcomes including a reduction in the need for surgery and hospitalization. Future goals may include avoidance of corticosteroids, prevention of stricture and fistula formation, prevention of extraintestinal manifestations and decreased costs of long-term care.

Changing the goals of treatment requires a change in treatment strategy. Conventional approaches have been based upon ‘clinical outcomes’ using a ‘bottom-up’ strategy with conservative use of immunomodulators. Current aims have included the induction and maintenance of clinical remission, prevention of disease and therapy-related complications, the optimization of surgical outcomes and prevention of post-operative recurrence. Future approaches are likely to personalize treatment based on the patient’s prognosis determined using biological predictors of response. Patients with a poor prognosis will receive early-aggressive therapy; additional goals will be disease modification, improved pharmacoeconomic outcome, and eventually disease prevention.

3. Clinical application of IBD research
Current research goals include improvement in the monitoring and treatment of IBD, and prediction of outcome. This will allow optimization of therapy and identification of patients who will gain the most benefit from aggressive therapeutic strategies. Some research outcomes may be applicable in clinical practice today.

3.1. Monitoring disease progression and response to treatment
Until recently, the standard approach to monitoring IBD status has been based largely on clinical symptoms. The need for biomarkers to monitor disease progression and response to treatment in IBD has long been recognized and their use in other chronic diseases is well established. For example, in Type 2 diabetes, blood glucose monitoring and blood pressure control have been shown to reduce the risk of complications. In IBD the ideal would be to have a non-invasive marker that correlates well with intestinal inflammation and lesions, predicts flares, responds to appropriate treatment changes, and is user-friendly and affordable.

Faecal calprotectin fulfils some of these criteria. On a practical level, the need for stool sampling may be seen as a drawback, but this is outweighed by the assets – calprotectin correlates with endoscopic lesions and can predict relapse. In addition, levels of calprotectin change in response to treatment. In clinical practice, measurement of calprotectin is practical, as it is a stable biomarker requiring only small amounts of stool, and rapid tests are in development.

Technical and strategic issues need to be addressed before the wide-spread use of calprotectin as a biomarker is possible. Technical issues include reproducibility, availability, user friendliness and rapidity of results. Inter-kit correlations are not known and intra-kit reproducibility may also be a challenge. The development of rapid tests allowing the use of a single stool sample from one patient (rather than multiple samples required in a full ELISA plate) may have great logistic advantages, and preliminary data indicate a good correlation with classical ELISA.

Strategic questions include whether to use calprotectin alone or in combination with C-reactive protein (CRP), its suitability for all patients, the optimal testing frequency, and how to best use calprotectin in decision making in clinical practice. A combination of calprotectin and high-sensitivity CRP testing may have better predictive value for mucosal healing than calprotectin alone. Some evidence suggests that monitoring calprotectin every 2 months, rather than once a year, in Crohn’s disease patients in remission, can detect a relapse 4 months before it occurs. Similar results have been observed in ulcerative colitis (UC) patients – monitoring calprotectin every month in patients in deep remission predicted relapse 4 months before it occurred.

In clinical practice, the combination of biomarkers may help to decrease the need for endoscopic monitoring. This would be particularly helpful for patients in clinical remission when there is doubt about mucosal healing, or to ensure that the disease is under control in patients at high risk of relapse and complications; raised calprotectin levels in these patients would prompt further investigation and optimization of therapy. A meta-analysis of 551 patients demonstrated that a combination of faecal calprotectin and CRP, used at appropriate thresholds, could avoid up to half of colonoscopies without hampering the prediction of relapse.

In future, patient-based monitoring of calprotectin could be implemented. Two new rapid faecal calprotectin quantitative tests have been compared with ELISA and their
feasibility for home testing is being investigated. The first test uses a scanner linked to a laptop computer loaded with special software to read the result, while with the second test a photo taken with a mobile phone is sent to the laboratory and the result appears on the mobile phone screen after 15 seconds. Patients could self-measure calprotectin every 2–3 months and, in consultation with the IBD nurse or physician, use the results to adapt and optimize therapy. This scenario has the advantages of enabling tight disease control and empowering patients.

3.2. Optimizing current therapies

After 3 decades of research into the genetics of IBD, over 160 independent IBD susceptibility loci have been discovered. However, the promise of increased genetic understanding translating into clinical practice has, in general, yet to materialize. One notable exception is the knowledge of the pharmacogenetics of thiopurine metabolism, which can be manipulated to optimize the use of currently available treatments.

The mechanisms of biotransformation of azathioprine to thioguanine nucleotides and the role of thiopurine methyltransferase (TPMT) have been extensively studied. TPMT inactivates 6-mercaptopurine (6-MP) to form methylated metabolites in competition with two alternative pathways that convert 6-MP to thiouric acid (catalyzed by xanthine oxidase) or to the active metabolite, thioguanine nucleotide (TGN), which is catalyzed by cytosolic enzymes. The formation of high levels of methylated metabolites results in the phenotype of hypermethylation. These data are being applied in clinical practice to guide the treatment of patients with IBD. TPMT activity demonstrates a polymorphic distribution in patients with IBD (Fig. 1) and can help to predict which patients are likely to respond to therapy or experience toxicity, thus enabling personalization of treatment.

The TPMT pathway can be manipulated in two ways. In the first, azathioprine dose reduction allows safe and effective treatment in patients with intermediate TPMT activity; however, in those with normal or high TPMT, personalizing treatment is less clear as hypermethylation is not predicted by TPMT levels. There are two patterns of hypermethylation defined by the levels of the metabolites TGN and methyl mercaptopurine (MMP): patients who have low TGN levels with high MMP are less likely to respond to azathioprine therapy; those with normal TGN and high MMP are more likely to experience side effects. Distinct genotypes have been identified in these two hypermethylator patient phenotypes. This may allow identification of people who are likely to hypermethylate prior to commencing therapy.

If hypermethylation can be predicted, it would be possible to use the second manipulation of the TPMT pathway in advance rather than waiting for hypermethylation to happen. This uses allopurinol in combination with reduced-dose azathioprine to circumvent thiopurine hypermethylation and achieve a reduction in disease activity in thiopurine-resistant patients. However, the mechanism is not well understood. Allopurinol does not directly inhibit TPMT; it inhibits xanthine oxidase via an alternative thiopurine pathway leading to the formation of an intermediate metabolite, which then inhibits TPMT. Understanding of these biochemical mechanisms may further improve the safety and effectiveness of thiopurine treatment by novel manipulation of thiopurine metabolism. In addition, ongoing collaborative research in the UK aims to identify genetic markers in patients at increased risk of developing toxicity to thiopurines.

3.3. Ongoing research studies

While it is possible to apply some of the research advances in clinical practice today, it is clear that further work is required. In the UK, targeted translational research assessing potential predictive genetic and serological factors for response and toxicity to anti-tumour necrosis factor (TNF) drugs is underway. In addition to continuing pharmacogenetic research, other innovative areas of research in IBD involve the use of gut microbiota – the most densely populated ecosystem on Earth. In addition to the direct use of microbiota as therapy with probiotics and faecal transplantation, targeting the microbiota may extend the use of current therapies, e.g. by targeting enzymes of the microbiota to alter drug metabolism with the aim of optimizing efficacy and reducing drug toxicity.
The probable involvement of microbiota in IBD is discussed by Travis et al. \textsuperscript{24} in this supplement. A further potential area of research may involve targeting the immunological dysregulation component of IBD, in particular aiming to develop targeted cell-based tissue-specific immunotherapy, obviating side effects of systemic immunosuppressants. It is worth remembering that managing IBD is not just about the treatment. Even when the disease is in remission many patients experience fatigue, faecal incontinence, pain and lack of food “enjoyment”; therefore a holistic approach to IBD management is required. Awareness of these symptoms is being raised and interventions to target iron deficiency, vitamin D deficiency, or osteoporosis are the standard of specialist care.

4. Improving standards of care for patients with IBD

In addition to the clinical application of advances in treatment and monitoring, the availability of new therapies for the treatment of IBD has raised expectations of improved outcomes, i.e., achieving and sustaining deep remission. The establishment of standards for treatment and service delivery, together with aligning process will help to achieve these aspirations.

4.1. Realizing aspirations by aligning standards in IBD clinics

At an individual patient level key actions taken by healthcare professionals at diagnosis and monitoring continuing care can help to optimize their care. Table 1 details some ‘golden’ key Do’s and Don’ts for managing individual patients with IBD.\textsuperscript{25–40} At an institutional level these aspirations can be met by aligning processes and standards of care. These should include a monitoring schedule that accounts for the different stages of the disease and a general safety assessment framework to help reduce the incidence of toxicity.

The golden Do’s and Don’ts link current goals of management of IBD with suggested implementation rules. These will obviously be modified as more data are available from important studies investigating alternative treatment strategies such as REACT (Randomized Evaluation of an Algorithm for Crohn’s Treatment),\textsuperscript{33} POcER (Post-Operative Crohn’s Endoscopic Recurrence),\textsuperscript{41} CALM (tight Control of disease Activity using CDAI, CRP and calprotectin Monitoring),\textsuperscript{32} the ADACAL study (calprotectin and hsCRP as markers of a new Diagnostic-therapeutic strAtegy that assesses muCosal Activity to individuaLize treatment, and improve the prognosis of patients with Crohn’s disease treated with immunosuppressants),\textsuperscript{31} etc. In order to treat to target and achieve goals, it is important that monitoring processes are aligned with the objectives (one such monitoring scheme is shown in Fig. 2).

In addition to ensuring a monitoring schedule is in place, a general safety assessment framework should be adopted to standardize the identification of patients in whom particular treatment approaches may be contraindicated. The framework should encompass a full patient history; a thorough physical examination; and where indicated, appropriate laboratory monitoring, and imaging. Realizing the goal of sustained deep remission in IBD patients can be helped by adopting a standardized approach that encompasses all the key disease management strategies.

4.2. Setting high standards with IBD ‘Centres of Excellence’

The delivery of care in IBD takes place in a variety of settings spanning primary and secondary care and ranging from individual clinics to large multidisciplinary centres. There is an increasing trend towards the establishment of so-called ‘Centres of Excellence’, which are expected to set and deliver a high standard of care. However, there are no criteria or ‘official recognition’ for IBD ‘Centres of Excellence’ and most are “self-proclaimed”.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Golden Do’s and Don’ts for the management of Crohn’s disease</th>
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<tr>
<td><strong>DO</strong></td>
<td><strong>DON’T</strong></td>
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<tr>
<td>• Consider not just disease severity at the time of assessment, but the disease anatomy and course to determine therapeutic strategy\textsuperscript{35}</td>
<td>• Use steroids longer than 16 weeks or more than once or twice a year\textsuperscript{36}</td>
</tr>
<tr>
<td>• Fully phenotype and risk-stratify patients at diagnosis to determine therapeutic strategy\textsuperscript{35–38}</td>
<td>• Use azathioprine as monotherapy – biologics are superior\textsuperscript{37}</td>
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<tr>
<td>• Assess objective disease markers, which are as important as clinical symptoms in guiding therapeutic strategy; current ongoing studies\textsuperscript{31–33} will inform optimal monitoring of Crohn’s disease activity</td>
<td>• Treat with biologics in the absence of objective evidence of inflammation\textsuperscript{37}</td>
</tr>
<tr>
<td>• Identify early the patients for intensive treatment\textsuperscript{34}</td>
<td>• Forget to vaccinate your patients; all recommended vaccinations, plus influenza, Human papilloma virus, Hepatitis A and B, pneumococcus, meningococcus (N.B: patients on immunosuppressive therapy [including biologics] should not be given live vaccines)\textsuperscript{38,39}</td>
</tr>
<tr>
<td>• Prioritize sustained remission over immediate response\textsuperscript{35}</td>
<td>• Discontinue effective therapy\textsuperscript{40}</td>
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Figure 2: Empiric monitoring scheme for patients with Crohn’s disease prescribed anti-TNF therapy. CEUS, contrast-enhanced ultrasonography; CRP, C-reactive protein; CT, computed tomography; F-CalP, faecal calprotectin.
The majority of international IBD ‘Centres of Excellence’ have an historical precedent of mentoring by leaders with an evolution of protégés. Expanding communication and connectivity leads to additional regional and local centres of expertise. In addition, there has been an evolution of collaborative clinical and research activities under the auspices of the Crohn’s and Colitis Foundation of America (CCFA; North America), the Groupe d’Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID; France and Benelux), the European Crohn’s and Colitis Organisation (ECCO) and other regional and national societies.

One consistent feature amongst the academic ‘Centres of Excellence’ is a combination of collaborative (within the centres) clinical and surgical expertise combined with clinical and/or basic science research. All have a track record of publication. Minimal criteria for ‘Centres of Excellence’ may be a dedicated commitment to patient care with medical-surgical partnerships. While basic and clinical research has largely been limited to larger centres, clinical trials are now expanding to regional and local centres.

The benefits to patients of such expert dedicated care are considerable: expanded resources to handle complex cases, including specialized surgery, nursing, nutritional and psycho-social care, patient advocacy and access to second opinions or consultations. Another evolving benefit to patients is participation in clinical research protocols, while the potential to participate in basic research portends future rewards for them. Healthcare professionals working in these centres benefit in several ways: through access to specialized and sub-specialized services and clinical trials of innovative therapies, and through potential to collaborate on research between centres.

Potential benefits to healthcare plans include reduced costs (the higher direct costs in tertiary centres are counterbalanced by reduced indirect costs, and improved quality via more efficient use of therapies or resources); the promise of better long-term outcomes (economics); and the availability of clinical trials. Even the industry benefits, as clinical expertise can avoid inappropriate recruitment to clinical trials that impairs the ability of trials to demonstrate a difference.

5. Innovative collaborative ideas to advance IBD management

The world is complex for patients with IBD; not only must they interact with nurses and physicians, but also with authorities, companies, patient associations and scientific societies. Cooperation is a key driving force in evolution, including human evolution.42 Collaboration could help patients on an individual level and help to reduce the social burden of the disease. The management and understanding of IBD can be improved through collaborative efforts between IBD organizations as well as through co-operative efforts across organizations, countries, and globally.

5.1. Collaboration: Reaching the society level

Several approaches are being taken to improve the quality of care for patients with IBD and increase awareness of the disease. The quality improvement benefits of ‘Centres of Excellence’ are demonstrated by the following examples of collaborative efforts. The Pediatric IBD Network (Improve Care Now) in the USA43 has improved process measures such as monitoring of growth and nutritional status. The IBD Standards Group in the UK44 ensures that patients receive good quality disease information and support. ECCO develops evidence-based patient management guidelines and consensus statements.45,46 The Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) and the Asociación de Enfermos de Crohn y Colitis Ulcerosa (ACCU) in Spain47,48 develop guidelines and disseminate information on IBD in a permanent collaboration between patients and healthcare providers. Other examples are the American Gastroenterological Association (AGA) and CCFA Quality Improvement Initiatives.

In addition, a collaborative initiative is starting, led by the European Federation of Crohn’s and Ulcerative Colitis Associations (EFFCA) in collaboration with ECCO, in a new project to fight against the social burden of IBD through a combination of science, awareness and control. The project will be sustained by multiple stakeholders, including patients, clinicians, investigators, international and national medical societies, and the pharmaceutical industry, all working with international and national patients associations. The strategy will be to improve disease awareness and social relevance, to elevate standards of care. A collaborative platform is being launched in Barcelona on February 15th (to coincide with the 7th Congress of ECCO), specifically to raise autoimmune disease awareness, starting with a specific focus on IBD. Specific engagement follow-up activities are planned.

5.2. Collaboration: Reaching the global level

Inflammatory bowel diseases have become a rapidly expanding and dynamically changing challenge. While a global approach to CD and UC is desirable, the majority of current knowledge about the disease is based on information from the Western World.49,50 Moreover, the known inter- and intra-country differences in incidence and prevalence can only be explained in part by genetic variation.50 Epigenetic factors are not fully understood and can be studied best in emerging nation cohorts, in migrant cohorts from emerging nations and by comparison with well-studied Western cohorts. Global differences in disease epidemiology, phenotype, course, availability of diagnostic testing and medications as well as professional qualification may also impact on diagnosis and management strategies.51,52

It is time for a truly global research and communication platform to take on this challenge. IBDMAP (www.ibdmap.org – Spatial Epidemiology of Crohn’s and Colitis; Fig. 3)53 aims to collect, process, provide and update comprehensive epidemiological data on IBD and its care all over the world, taking advantage of internet geocoding and novel data mining through computer visualization technologies. The ultimate goal is to analyze and present the information in a four-dimensional manner, i.e., in addition to graphical spatial epidemiology with interactive maps and overlays, a timeline will be created to track the changing disease and practice patterns. With this approach it is hoped to better understand epigenetic factors and raise global awareness of these diseases.
This project was inspired by the World Digestive Health Day (WDHD) on Inflammatory Bowel Disease organized by the World Gastroenterology Organization (WGO). The WGO, a federation of 110 national societies of gastroenterology, serves as the Global Guardian of Digestive Health. All clinicians, professional societies and patient organizations involved in IBD are encouraged to help develop this project and their input is critical to its success. The benefits of participation in the project will include open online access, shared authorship on future journal publications and opportunities to participate in associated events.

6. Summary

In spite of the availability of several strategies for the optimization of IBD management, there is a need for the standardization of care across different settings. We have proposed several different approaches that can be implemented to optimize the management of IBD in practice today, both locally and at a wider society and global level. We have also highlighted some potential future innovations.

The achievement of the current treatment goals would be facilitated by biomarkers such as faecal calprotectin, alone or in combination with CRP, and the manipulation of the thiopurine pathway to increase the reach of current medications. Raising standards of care can improve the patient experience through standardized approaches to management and possibly through the establishment of ‘Centres of Excellence’. Best practice can be shared through collaboration between patients, IBD organizations and pharmaceutical companies working together to improve care and outcomes. The IBDMAP project may help give us a global picture of the disease and healthcare facilities. This improved knowledge may be used to increase our understanding of the disease and help policy makers plan for better healthcare of patients with IBD.

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