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Prognostic modelling in IBD

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ABSTRACT

In the ideal world prognostication or predicting disease course in any chronic condition would allow the clinician to anticipate disease behaviour, providing crucial information for the patient and data regarding best use of resources. Prognostication also allows an understanding of likely response to treatment and the risk of adverse effects of a treatment leading to withdrawal in any individual patient. Therefore, the ability to predict outcomes from the onset of disease is the key step to developing precision personalised medicine, which is the design of medical care to optimise efficiency or therapeutic benefit based on careful profiling of patients. An important corollary is to prevent unnecessary healthcare costs. This paper outlines currently available predictors of disease outcome in IBD and looks to the future which will involve the use of artificial intelligence to interrogate big data derived from various important 'omes' to tease out a more holistic approach to IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a highly heterogenous inflammatory condition of the bowel which is increasingly prevalent, with an expectation that it will affect 1 % of the UK population by 2026 [1]. IBD comprises mainly ulcerative colitis (UC) and Crohn's disease (CD) and results from an abnormal immune response [2] to an environmental disturbance [3] in those with a genetic predisposition to mount such a response [4]. IBD represents the paradigm of auto-immune disease in which an imbalanced internal gut environment resulting from (largely poorly understood) dietary changes in the post-industrial external environment (exposome) drives a first local innate and then chronic latent systemic immune response in patients. This is a highly complex and individualised immune response involving personal and various and variable environmental factors as well as the involvement of a plethora of tissues at the molecular level. This complexity, coupled with a current lack of understanding regarding basic molecular pathophysiology underpinning IBD means that our current prognostic ability in this condition limited.

Prognostic modelling in IBD is complicated by the heterogeneous nature of the disease manifesting as largely either CD or UC and the fact that underpinning environmental influences change over time [5]. IBD studies suffer from a lack of agreement regarding clinical outcome measures and various are used. The 'gold standard' with respect to the efficacy of IBD treatment is mucosal healing but this, entailing repeated endoscopy, is onerous and potentially harmful for the patient, resource-heavy for the health service and impractical particularly in CD as the small bowel is inaccessible to direct visualisation. Furthermore, the narrow and short-term outcomes chosen in interventional trials assessing potential novel treatments for IBD don't reflect the complex, changing and life-long effects of the disease on patients. In this context the recent International Organisation of IBD (IOIBD) Selecting Endpoints for Disease Modification Trials (SPIRIT) initiative developing a consensus on more meaningful outcomes based on objective holistic patient centred measures represents a positive step forward and should improve future prognostic biomarker discovery [6]. Many biomarker studies in the literature are not hypothesis driven but associative and retrospective [7] and all too often potentially useful biomarkers discovered are not validated in second validation cohorts [8].There is also a problem with timing in that as well environmental influences, the intestinal immune cell milieu changes over time switching from an early Th1 dominance to Th2 pro-repair phenotype [9] so that different mechanisms are in play as inflammation is initiated and proceeds. This would potentially explain the paradoxical disconnect seen between successful early resolution of inflammation not associating with expected positive long-term outcomes in many patients with CD, alongside the observation that despite new and powerful immune-suppressive treatments UC patients still regularly come to surgery [10,11].

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Furthermore, regarding biomarker studies of IBD in adults at least, there is a dearth of longitudinal studies based on inception cohorts which are not confounded by treatments. In this context the paediatric literature is more informative with precious few studies in adult inception cohorts.

2. Currently available predictors of disease outcome

2.1. Clinical

Clinical features such as age, disease phenotype at presentation, extra-intestinal manifestations and behavioural factors such as cigarette smoking have been studied particularly in the context of Crohn's disease. Thus, the presence of peri-anal and ileal disease, age (under 40) and the use of steroids at diagnosis has been linked with poor outcome [12]. Similarly smoking and severe endoscopic appearances at onset have been associated with poor outcome [13] whereas not smoking and the presence of rectal sparing has been linked with a better outlook [14]. On the other hand, and somewhat paradoxically, smoking is protective against UC relapse [15].

Regarding UC, age under 40 at diagnosis, female sex along with extraintestinal manifestations signal relapse whereas men with more extensive disease are more likely to need colectomy [11]. Early first relapse in UC is a marker of poor outcome [16] whereas, as would be expected, mucosal healing in UC is a positive marker of future outcome [17].

These observations, while valid and important, come from observational retrospective studies and so provide evidence of association but are not of clinical use for prognostication.

Recently Waljee and colleagues took a random forests-based machine learning (ML) approach using decision trees to develop predictive algorithms based on baseline and week 6 clinical data on patients with both UC and CD in the large GEMINI vedolizumab program. Splitting their results into training and testing cohorts they were able to predict with considerable accuracy corticosteroid free clinical remission at week 52 in both UC [18] and CD [19]. This approach used standard parameters such as baseline physiological measurements, previous drug exposure, biochemical markers coupled with interventional drug levels to achieve useful clinical predictive models. This work needs validation in other cohorts but is a good example of the future possibilities of applying artificial intelligence (AI) in the search for prognostic indices using parameters measured in routine clinical care.

2.2. Genetics

The last couple of decades have seen great progress in identifying (more than 240) genetic loci associated with IBD both in CD [20] and UC [21]. Many of these studies identified single nucleotide polymorphisms (SNPs) that code for proteins key to mediating the interface between the gut microbiome and the innate immune system. Perhaps the most promising SNP discovered in this context was nucleotide-binding oligomerisation domain containing protein 2 (NOD2). This epithelial protein recognises intracellular muramyl dipeptide (MDP) a component of the bacterial cell wall [22]. The interaction between the epithelium and bacteria promotes activation of the innate immune response. Frameshift and missense mutations of NOD2, leading to aberrant bacteria/cell wall interaction have been clearly linked with the pathogenesis of Crohn's disease. However, an attempt to create a genetic risk score based on allelic load with respect to the recognised disease associated SNPs only accounted for a fraction of the observed phenotype [23]. While on the face of it this highlights the disappointing clinical utility of genetics in terms of predicting outcomes in the clinic, these studies have nevertheless led to many discoveries regarding the inter-woven pathophysiological pathways driving enteric inflammation including microbiota sensing, barrier function, innate and adaptive immune signalling, fibrosis and cellular homeostasis [24].

A recent agnostic approach taken to the analysis of genome-wide association study (GWAS) data from 2734 IBD patients identified 4 distinct loci (FOX03, IGFBP1, XACT and MHC region between HLAB and HLA DR genes) associating strongly with disease phenotype [25]. Interestingly these 4 loci had not previously been linked with IBD. This illustrates the importance of using large data sets and agnostic analytical methods in this endeavour which, given the heterogenous nature of the pathology, is very prone in small data sets to dangerous overfitting of data.

Although the results from these GWAS studies are interesting with regard to providing pathophysiologic insights into IBD, the odds ratios of individual disease related variants are too low to be clinically useful [26]. However, progress continues to be made with new technology. Recent work applying machine learning algorithms to analyse published GWAS datasets to home in on IBD related gene sets has shown promise in detecting novel candidate risk genes [27].

Notwithstanding the low clinical utility accruing from this early work on genetic risk factors regarding disease prognostication (so far), recent work in the area of pharmacogenetics has started to highlight the importance of targeted genetic testing to predict response to, and adverse effects of, treatments used for IBD.

In this context testing for thiopurine methyltransferase levels prior to the initiation of thiopurines has long been adopted into clinical practice, as low levels will lead to adverse effects from treatment particularly haematological side effects [28,29].

More recent GWAS studies have identified that carriers of polymorphisms in Nudix hydrolase 15 (NUD15), which are prevalent in European and South Asian populations [30] are highly susceptible to myelosuppression after thiopurine initiation, this mutation accounting for about half of all cases of neutropenia [31]. Accordingly, testing for NUD15 has, in addition to TPMT, been recommended routinely for patients in whom thiopurine therapy is planned [32].

Genetic polymorphisms from the large UK personalised anti-TNF therapy in Crohn's disease study (PANTS) database have identified associations with thiopurine induced pancreatitis [33] and 5ASA-linked renal damage [34]. Other work from this group in 955 UK patients of largely European ancestry-showed that 40 % of those of haplotype HLA-DQA1*05 had antibodies to antiTNFa, implying that carriers of this HLA marker may be prone to treatment failure due to the development of anti TNF monoclonal antibodies [35]. This observation is the focus of a current prospective Canadian trial INHERIT (NCT04109300) which aims to examine the utility of HLA-DQA1*05 testing prior to the initiation of anti-TNFa treatment.

2.3. Proteomics

i) CRP

CRP is a hepatic acute phase protein that is produced in response to IL6 release from macrophages and T cells and is a commonly used non-specific marker of inflammation in many conditions [36]. Henrisksen et al. demonstrated that serum CRP level greater than 10 mg/L one year after diagnosis was predictive of surgery in patients with Crohn's disease [37] and it has been shown that elevated CRP in Crohn's patients otherwise thought to be in clinical remission predicted hospital admission and risk of surgery [38]. In clinical practice CRP remains very useful for disease monitoring for individual patients particularly in CD given the systemic *trans*-enteric phenotype in comparison to the mucosal inflammation characterising UC [39]. However, its use as a single, generalisable prognostic marker is limited by the fact that expression is determined genetically, varies between individuals and it is not specific for IBD [40].

ii) Faecal Calprotectin (FCAL)

FCAL is a calcium and zinc binding heterodimeric protein derived

from neutrophils and widely used as a non-invasive marker of IBD activity. Its classical action as an innate immune protein is to deprive components of the microbiome access to transitional metals [41]. In clinical practice, owing to the continuous extensive colonic inflammation typical of UC rather than the patchy inflammation characterising CD, it is an accepted adage that FCAL correlates more closely with endoscopic activity in UC [42,43]. However, a recent meta-analysis examining the diagnostic accuracy of FCAL in predicting relapse in IBD highlighted its utility in CD [44]. From a review of 24 studies, the investigators identified a level of 152ug/g as optimal for predicting relapse with a sensitivity of 0.72 and specificity of 0.74. In this metanalysis FCAL showed similar performance for UC and CD. The utility of FCAL as a robust prognostic tool is limited by a lack of an agreed standard method of analysis and the fact that the level in faeces is dependent on bowel frequency and consistency.

iii) Other proteins

Recent work from the North American Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) cohort, a large prospective inception cohort study examining the risk of stricturing and penetrating disease in 913 children enrolled before treatment has undertaken a targeted analysis of 10 proteins linked with fibrosis in CD [45]. Comparing 58 children who developed fibro-stenosing disease with a matched cohort who didn't, the authors uncovered a particular candidate protein extracellular matrix protein I (ECM1) which had a PPV and NPV of 79 % and 74 % with sensitivity and specificity 80 % and 71 % for the prediction of developing fibrosis in 3 years from disease onset. More recently, applying a machine learning approach to examine blood samples taken from the RISK cohort, investigators identified novel proteomic profiles which out-performed both clinical and serology-only models in predicting complications in this cohort [46]. This and the previous study highlighting ECM1 awaits prospective validation in a separate cohort.

2.4. Microbial Markers

i) Serological markers

Serological markers of immune response to enteric pathogens have long been of interest as potential prognostic indicators in IBD. For example, antibodies against neutrophils have been demonstrated in the peripheral blood of patients with IBD, the best example of this being peripheral anti-nuclear circulating antibody-pANCA [47], which is found more commonly in UC than CD [48].

Similarly anti-Saccharomyces cerevisiae antibodies (ASCA) have been used as a diagnostic marker particularly in Crohn's disease [49]. It has been shown in a study demonstrating increased antimicrobial antibody expression before IBD diagnosis that ASCA expression is associated with more complex Crohn's disease and need for surgery [50]. Granulocyte Macrophage-Colony Stimulating Factor (GM- CSF) is produced by innate lymphoid cells (3) ILC (3) cells and these cells promote anti-bacterial and immune function. In CD myeloid cells differentiate into ILC (1) rather than ILC (3) leading to aberrant anti-bacterial and immune functions. In a prospectively followed cohort of North American (asymptomatic) forces personnel who went on to develop IBD it has been shown that antibodies against GM-CSF are detectable in people destined to develop CD up to 6 years before diagnosis [51]. Anti GM-CSF antibodies were associated with ileo-colonic disease location and conferred 2.8 risk hazard ratio of complicated penetrating or stricturing disease within 3 months of diagnosis.

E.coli has long been recognised as an important microbe in the pathogenesis of IBD [52]. Antibodies to E.coli outer membrane (OmpC) and antibodies to flagellin (CBir1) have been linked to disease complexity [53]. In the RISK paediatric inception cohort, expression of 2 or more microbial associated antibodies in serum was associated with a worse prognosis. The two particularly implicated with a poor prognosis were ASCA and CBir1 [54].

These serologic studies highlight the importance of the interaction between the microbiome and the innate immune system in the pathogenesis of IBD. The utility of these markers in the early phase of disease is hampered by the retrospective, associative nature of the published work and by the important fact that seropositivity diminishes with time in individual patients [55]. These older serological markers are likely to be surpassed by the more granular information regarding the role of the gut microbiome which is currently accruing at pace.

ii) The microbiome and metabolome

Interest in the role of gut bacteria in the pathogenesis of IBD is long standing. As far back as 1950, in the first recognised description of a now established feature of UC, Seneca and Henderson described the increase in coliforms observed in this patient cohort [56]. This was taken further by Gorbach et al. who used culture-based techniques in patients at IBD presentation to demonstrate that increases in Coliforms were associated with more severe disease and poor response to treatment [57]. They also noted that the composition of the microbiome in those with severe disease was further removed from that seen in health compared to those with mild disease.

Following this earlier pioneering work using traditional culture-based techniques the key importance of the gut microbiome in the pathogenesis of IBD has been uncovered in the last couple of decades. This owes to the advent of culture-independent high throughput genetic sequencing techniques coupled with rapid advances in bio-informatic technology for the analysis of large biological datasets. Core characteristics of the gut microbiome include the overall diversity of the microbiome, typically described as Alpha diversity (the overall structure of the community and the number of different microbial groups present) and Beta diversity (which attempts to quantify the difference between two ecosystems, for example health and disease). Microbiome sequencing technologies now available allow analysis of not only the structure, but also the function of the gut microbiome. The commonest technique utilised to date has been metaxonomics, most frequently sequencing conserved domains of the microbial 16S rRNA gene. Whilst microbial function can be inferred from data accruing from 16S rRNA sequencing, the development of shotgun metagenomic sequencing (automated whole genome Sanger sequencing) has allowed definitive establishment of all of the microbial genomes that are present in a given sample. This allows accurate analysis of not only microbial composition but also function. The field, however, should be considered 'in its infancy' and so is not without pitfalls. There is no standardisation in experimental or statistical methodology and this results in at times contradictory conclusions. Furthermore, many taxa resulting from whole genome sequencing are as yet 'unidentified and studies that do not undertake correction for multiple testing risk grossly overestimating the significance of findings made. The study of the microbiome as a prognostic marker for IBD is also beset with the problem of great inter- and intra-individual variability and the natural variation of the microbiome with age and in relation to environmental influences [5,58]. Nevertheless, data is accumulating apace in this regard.

Studies focussing on response to therapy and the microbiome cannot do so without consideration of the metabolome. Its characterisation allows true establishment of microbial function. The relationships between microbes and metabolites such as bile acids cannot be separated in the maintenance of colonocyte health and intestinal barrier function.

In IBD, there are two ways to consider the formulation of treatment modelling. The first, and perhaps the most eloquent, is to go to the start of the disease. By taking patients at the point of diagnosis, analysing baseline characteristics, and correlating these with longitudinal outcomes it is potentially possible to identify those with an adverse disease phenotype from the outset and make treatment decisions accordingly.

The second is to take a cohort of IBD patients with established disease and to evaluate changes pre and post initiation in combination with longitudinal follow up. Attempts at this have been undertaken in both adult and paediatric cohorts.

a) Paediatric inception cohorts presenting treatment outcomes and modelling.

Currently the largest and frequently referenced characterisation of the paediatric microbiome in Crohn's disease was undertaken using the RISK cohort [59] some data from which has been described above. At the time of the original publication, this presented 447 newly diagnosed CD patients, alongside 221 symptomatic controls. Characterisation of both the mucosal and faecal microbiome was undertaken, using both 16S and metagenomic sequencing. Increases in *Enterobacteriaeceae, Pasteruellaceae, Fusobacteriaceae, Neisseriaceae, Veillonellaceae* and *Gemellaceae* were seen in CD, compared to controls with species level enrichment seen including *Veillonella parvula* and *Gemella moribillum*. Prominent depletion of *Bifidobacteriaceae* and *Clostridiales*, amongst others, was noted. On a species level, this included B*ifidobacteria adolescentis, dentum, longum* and *bifidum*. Other key species diminished in CD included *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *Roseburia intestinalis*. On a functional level, the differential abundance described was seen to associate with an increase in glycerophospholipid and lipopolysaccharide metabolism alongside reduction in bile acid and amino acid biosynthetic pathways. The original report did not describe taxa associated with treatment outcome but did present a machine learning model. This was based on 90 % of the cohort and was able to predict 6- month outcome in the remaining 10 % with 67 % accuracy. The lack of detail in this regard became more apparent subsequently, when a far more detailed analysis of predictors was published three years later [54]. Here, the authors identified that higher baseline levels of *Ruminococcus* (stricturing) and *Collinsella* (penetrating) associated with disease complications, with the opposite true of *Rothia* (stricturing). *Veillonella* was paradoxically reduced in stool and the rectal mucosa, but increased in the ileal mucosa of those with penetrating disease. More detailed predictive modelling was undertaken in this study but unfortunately (despite the earlier work undertaken) did not include microbial parameters due to a smaller cohort having this data available. A smaller cohort seeking to predict outcome in CD was reported by Douglas et al. [60]. This included 20 CD patients and 20 symptomatic controls, also utilising the RISK cohort for validation. Alpha diversity was significantly reduced in CD relative to controls. A random forest model was utilised to classify disease state and treatment response. Using the microbial datasets, the 16S data at genus level was able to classify disease state at 84.2 % accuracy. For the metagenomics, the highest accuracy was at strain level (68.4 %). The most informative 16S genera were *Desulfovibrio, Akkermansia* and *Butyricimonas* whilst for metagenomics the strains were *Alistipes putredinis, Clostridium symbiosum* and *Faecalibacterium Prausnitzii.* Regarding treatment response, patients received 'real world' treatment without a set protocol. They were categorised as 'sustained response' or 'non-response' which 16S genera were able to classify response with 77.8 % accuracy, with the top performers being *Dialister, Bilophila* and *Aggregatibacter*. For metagenomics (at strain level) the accuracy was 72.2 % with *Paracteroides merdae, Sutterella wadsworthensis* and an unclassified *Lachnospiraceae* most valuable. Models were also run to be combined with microbial function, either measured (metagenomics) or inferred (using PICRUSt). Combining 16S and metagenomic datasets, inclusive of overall abundance and function, it was possible to predict treatment response with a 94 % accuracy.

In UC, the largest paediatric cohort studies also originated in North America. Two key manuscripts have arisen from the Predicting Response to Standardised Paediatric Colitis Therapy (PROTECT) cohort. By undertaking mucosal biopsies at baseline and at 12 months, alongside faecal samples at multiple time points, and subjecting these to 16S sequencing, it was possible to delineate significant associations with treatment outcome. The first paper [61] included 405 UC patients. At baseline, reduced alpha diversity (determined by the Chao1 metric) was associated with increased disease severity. Also at baseline, shifts in over 50 operational taxonomic units (OTUs) were associated with disease severity. In those who progressed to refractory disease over the course of treatment, differential abundance of 21 OTUs was seen at baseline. This included increases in the abundance of *Veillonella dispar* and *Haemophilus parainfluenzae.* Depletion was seen in *Ruminococcaceae*, *Dorea* and *Blautia.* Furthermore, steroid free remission at week 52 was associated with a higher abundance of *Ruminococcaceae* and *Oscillospira,* with lower abundance of *Sutterella* and *Eggerthella lentha.* A year later, the cohort had grown to 467 UC patients and a further manuscript exploring predictive modelling in more depth was published [62]. This paper also presented microbial profiles associating with an escalation to an anti-TNF treatment by week 52. Depletion of *Faecalibacterium prausnitzii* is seen in this cohort across several OTUs, alongside depletion of *Blautia, Bacteroides ovatus, Dorea, Bifidobacterium, Oscillospira* and *Coprococcus.* Increases were seen in *Haemophilus influenzae and Parainfluenzae, Campylobacter* and *Megasphaera.* The authors initially developed a multivariable logistic regression model to predict 52-week corticosteroid free remission using baseline clinical and demographic parameters including CRP, faecal calprotectin, histology and serology. To account for missing data across predictors, the cohort was reduced to 100 datasets assuming data was missing at random. By adding biological parameters relating to gene expression (antimicrobial peptide gene signature, transport and antimicrobial gene signature) and microbial abundance (specifically *Ruminococcaceae OTU 560535 and Sutterella OTU 589923)* it was possible to increase the area under the curve (AUC) of this model from 0.68 to 0.75.

One study presents work in a smaller mixed IBD cohort [63]. Across 19 patients (15 CD, 4 UC) and 10 controls, samples were taken longitudinally over 400 days. Both CD and UC demonstrated lower baseline alpha diversity than controls. This difference was not replicated in responders vs non responders to treatment. Coprococcus was lower in non-responders compared to responders. Predictive modelling highlighted this, alongside the suggestion of lower abundance of *Blautia* and *Lachnospira,* with increased abundance of *Veillonella.* The model in this paper was also a random forest model and used only microbiome data, carrying an AUC of 0.75.

b) Paediatric cohorts assessing specific interventions.

Within the paediatric setting, studies characterising the microbiome are often accompanied by an intervention in the form of corticosteroids or exclusive enteral nutrition (EEN). There are a number of studies in this area, some of which present pure inception cohorts, whilst others present mixed pre and post treatment. A Dutch paediatric inception cohort studied the impact of EEN on a cohort of 43 patients with CD, 27 of whom contributed to the microbiome analyses [64]. Significantly different baseline beta (but not alpha) diversity was seen in those who responded to EEN vs those who did not. Interestingly, taxa typically associated with health including *Dorea longicatena, Blauti obeum* and *Bifidobacterium longum* were associated with a lack of response. These changes were accompanied by metabolic changes including a higher baseline level of histidine, citrulline and isoleucine in those who subsequently responded. No baseline differences were seen in bile acids.

A similar study was undertaken with EEN in a Chinese cohort of 31 CD patients [65]. Again, significant reductions in alpha diversity were seen in CD relative to controls at baseline. However, it was also noted that those who went on to respond to EEN had a higher baseline alpha diversity than non-responders. Despite this field change, the only genus level significant difference was in *Ruminococcus,* which was seen in higher abundance in non-responders (but unusually was completely absent from responders despite being present in healthy controls). The small cohort and the lack of statistical rigour, with no clear correction

for multiple testing, further limits the significance of this finding.

Whilst these papers deal with exclusively pre-treatment patients, studies have evaluated response both to EEN and other therapies in mixed cohorts. Michail et al. [66] undertook an early study in this area in 2012. In patients with acute severe UC, the response to corticosteroids was analysed in 27 UC patients. Whilst 44 % of these were newly diagnosed, faecal samples were not obtained until the third day of treatment. They were compared with 26 healthy controls and once again it was possible to demonstrate a significantly reduced alpha diversity in the UC cohort. Non responders to corticosteroid therapy had a significantly reduced number of observed microbial 'phlyospecies' at baseline relative to responders. Significant differences in taxa abundance were not presented here. Lewis et al. [67] enrolled 85 CD patients with short disease durations embarking on escalated therapies (52 anti-TNF, 22 EEN, 16 PEN) after initial management. Whilst alpha diversity was reduced across all CD patients, they were subsequently clustered accordingly to severity of dysbiosis ('near' being closer to health). Response rates to anti-TNF were the same across both the near and far clusters (66.7 % vs 60 %).

Hart et al. [68] looked at the effect of EEN therapy in 20 CD and 10 UC patients. Whilst baseline differences were not explored in depth, it was noted that diversity was an early predictor of remission at the end of therapy. Indeed, alpha diversity levels were significantly higher in those who achieved remission at the end of treatment as early as week 2. This was true in both EEN and steroid groups. Jones et al. [69] explored machine learning in the context of predicting response to EEN. Across a cohort of 22 CD patients (18 treatment naïve) baseline microbiome data from 16S sequencing, metagenomic functional pathways and KEGG orthologs derived from faecal samples were combined with clinical data. Again, random forest models were developed using different components of the data. By combining amplicon sequence variants (ASVs), species richness and disease location and behaviour at diagnosis, response to EEN could be predicted with an AUC 0.9. The most informative taxa were *Ruminococcaceae UCG-002, Lachnospiraceae NK4A136, Bacteroides* and *Parabacteroides.*

c) Predicting outcome in adult cohorts

IBD inception is relatively under-explored in adult cohorts relative to the work done in paediatrics. One study does attempt to model outcome in an adult inception cohort [70]. 48 UC patients were classified as having a mild or moderate/severe disease course during follow up according to flare frequency and severity. However, only 18 provided samples at diagnosis. Using the commercially available GA-map dysbiosis test (Genetic Analysis AS, Oslo) it was possible to show in this small cohort that higher abundances of *Proteobacteria* and *Streptococcus* were seen at baseline in those with a subsequent moderate/severe course. Higher abundance of *Akkermansia* associated with an increased likelihood of a mild disease course. Mucosal antibacterial response profiles were characterised using an mRNA array of mucosal biopsies. Higher expression of CXCL2 was seen in those with a moderate/severe disease course, with BPI and CHUK increased in those with a mild course. Coupling this data together did not improve predictive ability, though the antibacterial response profile alone was able to discriminate between disease course types. The only other adult inception study also utilises the GA-map dysbiosis test.

There are an increasing number of studies that characterised response to given therapies in adult cohorts. These were recently evaluated in a large-scale systematic review of the area undertaken by Radhakrishnan et al. [71]. In accordance with paediatric studies of anti-TNF, two further studies have reported no significant differences in alpha diversity between responders and non-responders to Infliximab. Aden et al. [72] found that whilst infliximab therapy shifted diversity towards normal, baseline diversity did not predict response. However, predicted levels of butyrate and substrates involved with butyrate synthesis were predictive. Zhou et al. [73], examining changes in diversity according to response to antiTNFa treatment, were able to predict response with 86.5 % accuracy with microbial profile alone, increasing to 93.8 % with the addition of CDAI and calprotectin. The most informative microbial features of the model were several Clostridiales OTUs, which were also found to be enriched during response to therapy over longitudinal follow up. Ding et al. [74] aimed to integrate the microbial changes to that of the metabolome. Whilst baseline diversity did not predict treatment response, histidine levels were significantly higher in TNF responders, whilst circulatory lipid markers were also present in lower concentrations in responders.

Other than anti-TNF use, response to other biologics have also been studied. Ustekinumab responses have been characterised in a large cohort of 232 CD patients [75]. Increased alpha diversity was seen at baseline in responders, whilst *Faecalibacterium* and *Bacteroides* were more abundant at baseline in those who went on to achieve remission. Regarding Vedolizumab, in a cohort of 42 CD and 43 UC patients, alpha diversity was higher at baseline in those who went on to achieve remission, whilst *Roseburia inulinivorans* and *Burkholderiales* were more abundant. The signals were less clear cut in UC, though higher baseline abundance of *Streptococcus salivarium* did correlate with non-response [76].

At this stage, whilst microbial composition can differentiate health and disease, patterns can be contradictory. Machine learning models have made progress in predicting outcome using multi-omic datasets, but larger datasets are required, particularly with the ever growing armamentarium of treatment options available. It is hoped that upcoming large prospective studies such as IBD RESPONSE, a multi-centre UK study aiming to prospectively predict response to biologic therapies based on multi-omic datasets collected from patients prior to treatment will help to build our understanding in this fascinating area.

2.5. Transcriptomics

Recent developments in molecular profiling of tissue and blood show great promise in efforts to understand disease pathophysiology and to predict outcomes.

In the last couple of decades application of molecular profiling using transcriptomics to patient samples has led to considerable insights about predicting outcome based on baseline data. Thus, focussing on single tissue transcripts it has been possible to differentiate responders from non-responders in anti TNFa induction trials. For example, it was shown that high tissue expression of the cytokine Oncostatin M (OSM) and its receptor (OSMR) was predictive of treatment failure [77]. Similarly in a study of patients being treated with antiTNFa, lower baseline whole blood expression of Triggering Receptor Expressed on Myeloid cells 1 (TREM1) was predictive of response [78]. It seems that TREM1 expression reduces autophagy and monocyte differentiation in patients with CD [79]. This illustrates the potential for transcriptomic approaches in both developing prognostic biomarkers and understanding pathogenetic mechanisms/uncovering novel therapeutic targets.

In an investigation of patients undergoing vedolizumab initiation for IBD it was found that the baseline expression of four genes predicted endoscopic remission with 80 % accuracy in the training dataset and 100 % in the validation cohort. This powerful result is somewhat frustrated by the fact that very little is known about the function of these proteins (yet) [80].

These important insights from studies on treatments which have now become standard of care in IBD highlights the potential power of such an approach to enable the development of molecular profiling approaches which could facilitate individualised treatment strategies in the future. While these studies are based on retrospective analysis of stored biosamples in patients who have taken part in phase III pharmaceutical trials, another approach has recently been taken by investigators using a transcriptional gene signature profile as a prognostic marker in patients with first onset CD in the PROFILE study [81]. This exciting work is based on a previous investigation of CD8+T cell gene transcription in

patients with established IBD [82]. The investigators found that increased expression of antigen dependent T cell responses separated patients with increased disease relapse (in both CD and UC) from those with a more benign disease course. The investigators subsequently went on to use machine learning to develop a similar gene signature classifier based on a 17 gene model using CD8+T cells derived from active untreated IBD patients [83]. This was successfully validated in an independent cohort to demonstrate that the blood test was able to predict disease course in a dichotomous manner very similar to that seen in the previous tissue profiling [82]. It is on the basis of this clinically useful blood test that inception patients with new onset CD have been stratified to different treatment arms based on baseline CD8+T cell transcriptional gene signature. At the time of writing PROFILE has finished recruitment and is in the analysis stage. The outcome of this study may provide very interesting insights into IBD and may provide a valuable tool for prognostic modelling and planning treatment in patients with CD in the clinic.

An important example of the potential utility of gene transcriptomic signatures in prognostic modelling in CD again comes from the RISK cohort [53]. Genes regulating extracellular matrix accumulation were induced at diagnosis in ileal biopsies taken from patients who later developed stricturing disease whereas genes driving acute inflammation were linked with progression to penetrating disease. It should be noted that the ileal gene signature was from biopsies taken from inflamed tissue only; uninflamed adjacent tissue was not examined. Furthermore, performance of the gene signature model was validated on the same cohort (with statistical manipulation). Therefore, the results may not be generalisable, but this clearly needs further study in other paediatric inception cohorts.

In a recent study examining non-inflamed tissue taken from patients undergoing routine post-surgical endoscopic surveillance following Crohn's surgery, machine learning using random forest technology was applied to successfully identify a 30 gene transcript profile which differentiated patients with i0 Rutgeerts score from others [84]. Patients with i0 Rutgeerts score post-surgery for Crohn's disease have the most benign prognosis and this work, were it to be translatable to peripheral blood mononuclear cells and, of course, replicated, represents a step towards non-endoscopic follow up which is currently the standard of care.

2.6. Imaging

CD represents a much more difficult condition to evaluate both for diagnosis and predictive evaluation than UC. The latter is entirely within the 'range' of direct endoscopic visualisation whereas Crohn's disease is more diffuse and variable in presentation. The first successful diagnostic imaging tool developed is the Lemann Index [85]. This was proposed as an integrated diagnostic modality-independent score based on integrating magnetic imaging, CT and endoscopy as appropriate. In the initial evaluation of this score an overall unbiased correlation coefficient between the Lemann Index and predicted investigator damage evaluation of 0.84 was achieved. This has subsequently been validated in a separate cohort [86]. Interestingly, investigator assessments of tissue damage varied considerably comparing the two studies. Recently, the IOIBD SPIRIT Initiative has endorsed the Lemann index and recommended that centralised assessments be used in future clinical trials [6]. Another patient friendly non-invasive and reliable imaging modality which has proved useful particularly in CD in the last decade is transabdominal intestinal ultrasound [87]. The drawback of this technology with respect to disease prediction is that it is highly operator dependent. A recent systematic review has highlighted that literature concerning intestinal ultrasound comprises poorly controlled and small studies with considerable bias. Nevertheless, consensus around definitions of clinical response as measured by intestinal ultrasound and definition of transmural remission/healing are emerging [88]. It is to be expected that these diagnostic modalities will develop fast in the near future aided by developments in artificial intelligence/machine learning and should become useful tools to predict disease response in IBD in the coming decade.

2.7. Therapeutic drug monitoring (TDM)

While clinical and other parameters described above largely aim to stratify patients with respect to their likely response to various treatments, the role of therapeutic drug monitoring at least in clinical practice, is well established now for thiopurines and anti-TNFa agents at least [89]. Unfortunately, TDM is often not part of the trial protocol in therapeutic trials in IBD whether commercial or not. Hopefully this will be addressed in the future.

In a large prospective study of demographic and clinical factors predictive of anti-TNFa failure in IBD adults from the UK (PANTS) [90] the only independent factor that came out with respect to prediction of ant-TNF response was serum drug levels. From this study the development of antibodies against the drugs were associated with low levels.

Following the initiation of thiopurine treatment monitoring of metabolites, thioguanine nucleotides (TGN) and methylmercaptopurine (MeMP) is standard practice to assess adherence to treatment, suboptimal dosing and hypermethylation [89].

With the increasing armamentarium anti-cytokine and -integrin therapies for IBD

accumulating prospective real-life data will, in the future, undoubtedly extend the routine use of therapeutic dose monitoring beyond the current practice of measuring anti-TNFas and thiopurine metabolites [91].

3. Summary and future horizons

The growing acquisition of large multi-omic IBD datasets, alongside rapid developments in the ability to apply bioinformatics to big data is rapidly increasing our understanding in IBD. The burgeoning development in agnostic machine learning artificial intelligence applications give us the potential of developing powerful predictive tools and the simultaneous acquisition of new insights in the pathophysiology of this complex condition in the near future.

At present however, neither novel biomarkers based on the various 'omes' making up the IBD interactome nor imaging scores are 'fit for the clinic' [92]. Perhaps the tool potentially closest to clinical utility at present is the CD8+T cell gene signature which is being evaluated in a prospective clinical trial in CD at present [81]. As discussed in a recent ECCO workshop, the key to reaping the exciting potential of the vast amounts of mechanistic data being generated in IBD is a collaborative approach to the development of well curated large, longitudinally sampled, publicly available datasets [93]. There are several examples of such large collaborative projects at present such as the Horizon 2020 Initiative, Medicines Initiatives (IMI) projects and various others [94].

Future progress unravelling the IBD interactome will be based on a systems biology approach to the integration of large multi-omic datasets linked to good quality clinical metadata so that we move to a clearer understanding of the effect of the environment (exposome) on the highly symbiotic biological environment of the human gut over time [95].

Pharmaceutical-academic collaboration must be fostered so that biomarkers are incorporated into interventional trials for maximum impact, with all available data made public [93]. Any identified biomarkers or 'signatures' must be tested in independent validation cohorts.

Artificial intelligence is emerging as a very promising tool in IBD in relation to the large amounts of available digitised patient data which is highly amenable to computational methods needed for complex pattern recognition otherwise termed machine learning [96].

As mentioned above this machine learning using a random forests approach has been used with promising utility to predict outcomes in large phase III biologics trials [18,19]-

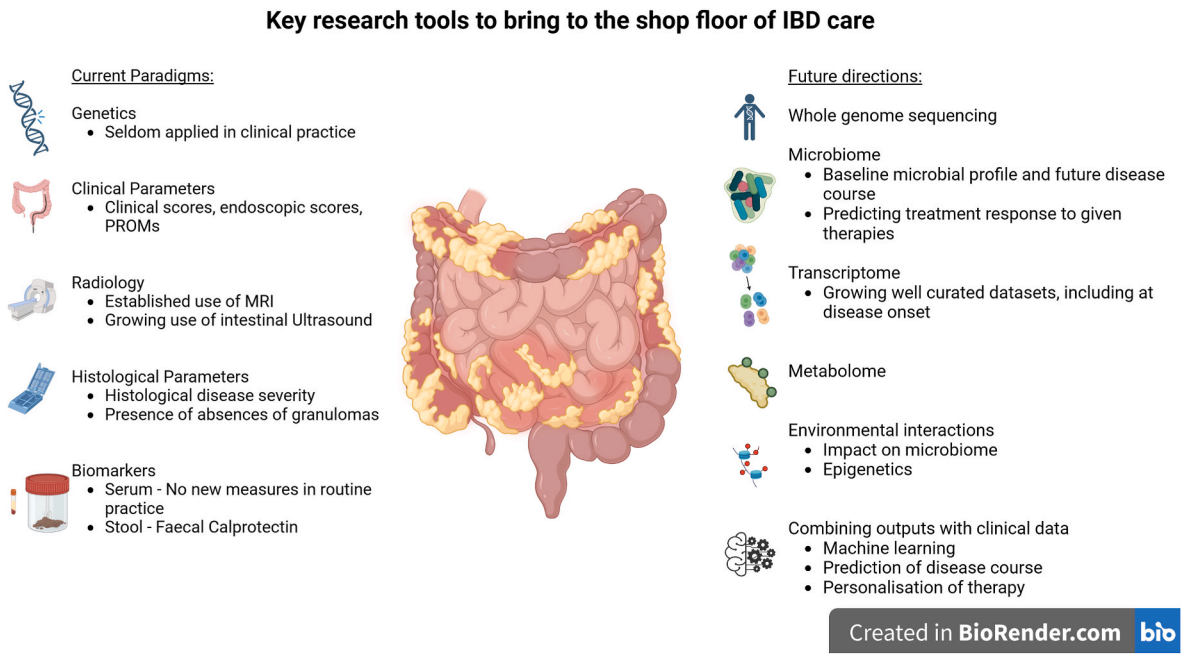

Fig. 1. IBD Clinical Horizons on the shop floor: The end of one size fits all.

The application of artificial intelligence in the development of multi-omic predictive biomarkers in IBD is developing rapidly. Another recent application of AI to help make sense of 'big data' in relation to IBD has been in the application of machine learning to prioritize IBD risk genes to detect novel IBD-associated genes using data from published GWAS studies [27,97].

It is likely that soon gastroenterologists in the clinic will be faced with multiple novel powerful predictive tools because of these endeavours [96]. While this is an exciting prospect it will take time for it to be applicable in the world of day-to-day clinical practice, inevitably entailing training in a new way of working and thinking. These horizons are summarised in Fig. 1.

Practice points

- Whilst microbial dysbiosis is established as a hallmark of IBD, the role for therapies seeking to manipulate the microbiome in IBD is yet to be well established.
- Protein biomarkers, such as faecal calprotectin, should represent a key monitoring tool in IBD outpatients.
- For those on anti-TNF alpha drugs, proactive use of therapeutic drug monitoring improves outcomes and prediction of durable response. The role for such monitoring for other biologics utilised in IBD is less well established.
- Modelling tools based on just clinical parameters are already able to demonstrate accurate prediction of given outcomes and will become a growing part of medical practice

Research agenda

- It has been demonstrated that data from particular omic domains can predict treatment response and outcome, but larger datasets are required for more robust signals.
- Powerful machine learning models need to be applied to the integration of large multi-omic datasets to draw out the key facets of the IBD interactome.
- Further research is required to determine how best to transform the findings of these large labour-intensive datasets into meaningful clinically deliverable actions that can improve outcome across real world clinical environments with finite resources.

CRediT authorship contribution statement

Peter Rimmer: Writing – original draft, Writing – review & editing. **Tariq Iqbal:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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