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POSITION STATEMENT

Precision nutrition in pediatric IBD: A position paper from the ESPGHAN special interest group for basic science and translational research, the IBD Porto group, and allied health professionals

Konstantinos Gerasimidis[1] | Richard K. Russell[2] | Federica Giachero[3] | Konstantinos Gkikas[1] | Balint Tel[4] | Amit Assa[5] | Jiri Bronsky[6] | Lissy de Ridder[7] | Iva Hojsak[8] | Andreas Jenke[9] | Lorenzo Norsa[10] | Rotem Sigall-Boneh[11,12] | Sara Sila[13] | Eytan Wine[14] | Matthias Zilbauer[15] | Caterina Strisciuglio[16] | Marco Gasparetto[17,18] | ESPGHAN Special Interest Group in Basic and Translational Research; the ESPGHAN IBD Porto Working Group; the ESPGHAN Allied Health Professionals

[1]Department of Human Nutrition, School of Medicine, University of Glasgow, Glasgow, UK

[2]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Royal Hospital for Children and Young People, Edinburgh, UK

[3]Department of Paediatric Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK

[4]Pediatric Center, MTA Center of Excellence, Semmelweis University, Budapest, Hungary

[5]The Juliet Keidan Institute of Pediatric Gastroenterology Hepatology and Nutrition, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Jerusalem, Israel

[6]Department of Paediatrics, University Hospital Motol, Prague, Czech Republic

[7]Sophia Children's Hospital, Erasmus MC University, Rotterdam, The Netherlands

[8]Children's Hospital Zagreb, University of Zagreb Medical School, Zagreb, Croatia

[9]Children's Hospital Kassel, University of Witten/Herdecke, Witten, Germany

[10]Pediatric Hepatology, Gastroenterology and Transplantation ASST Papa Giovanni XXIII, Bergamo, Italy

[11]Israel Pediatric Gastroenterology and Nutrition Unit, The E. Wolfson Medical Center, Holon, Israel

[12]Amsterdam University Medical Centers, Amsterdam, The Netherlands

[13]Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Zagreb, Croatia

[14]Department of Pediatrics, Division of Pediatric Gastroenterology, University of Alberta, Edmonton, Alberta, Canada

[15]Wellcome MRC Stem Cell Institute, University of Cambridge, Cambridge, UK

[16]Department of Woman, Child and General and Specialist Surgery, University of Campania “Vanvitelli”, Napoli, Italy

[17]Department of Paediatric Gastroenterology, Jenny Lind Children's Hospital, Norfolk and Norwich University Hospitals, Norwich, UK

[18]Norwich Medical School, Faculty of Medicine and Health Science, University of East Anglia (UEA), Norwich, UK

Correspondence
Konstantinos Gerasimidis, Department of Human Nutrition, School of Medicine, University of Glasgow, Level 3, New Lister Bldg, Glasgow Royal Infirmary, Glasgow G31 2ER, UK.
Email: Konstantinos.gerasimidis@glasgow.ac.uk

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Abstract

Stratified and precision nutrition refers to disease management or prevention of disease onset, based on dietary interventions tailored to a person's characteristics, biology, gut microbiome, and environmental exposures. Such treatment models may lead to more effective management of inflammatory bowel disease (IBD) and reduce risk of disease development. This societal position paper aimed to report advances made in stratified and precision nutritional therapy in IBD. Following a structured literature search, limited to human studies, we identified four relevant themes: (a) nutritional epidemiology for risk prediction of IBD development, (b) food-based dietary interventions in IBD, (c) exclusive enteral nutrition (EEN) for Crohn's disease (CD) management, and (d) pre- and probiotics for IBD management. There is scarce literature upon which we can make recommendations for precision or stratified dietary therapy for IBD, both for risk of disease development and disease management. Certain single-nucleotide polymorphisms related to polyunsaturated fatty acid (PUFA) metabolism may modify the effect dietary PUFA have in increasing the risk of IBD development. Non-colonic CD, mild-to-moderate CD, and high microbiota richness may predict success of EEN and may be used both for prediction of treatment continuation, but also for early cessation in nonresponders. There is currently insufficient evidence to make recommendations for precision or stratified dietary therapy for patients with established IBD. Despite the great interest in stratified and precision nutrition, we currently lack data to support conclusive recommendations. Replication of early findings by independent research groups and within structured clinical interventions is required.

KEYWORDS
exclusive enteral nutrition (EEN), inflammatory bowel disease (IBD), precision nutrition, prediction, stratified nutrition

1 | INTRODUCTION

Diet has long been implicated in the pathogenesis of inflammatory bowel disease (IBD), although this relationship is complex and difficult to decipher.[1] There is a wealth of past and ongoing research in diet associating with IBD, spanning from nutritional epidemiology, preclinical studies in animal simulant models of the disease, and more recent clinical trials.[1] Epidemiology points to potentially harmful and beneficial nutrients, from a Western and Mediterranean type, respectively, modifying risk of development of IBD.[1] Likewise, animal experiments implicate food industrialization and food additives in the instigation of gut inflammation, whereas clinical trials with dietary interventions have produced thus far variable signals of clinical effectiveness.[1]

Despite the major advances modern medicine has made in the treatment of patients with IBD, a significant proportion of patients will not respond to contemporary drug therapies. Likewise, response to a drug or dietary treatment can be variable and often depends on the measure or biomarker of disease activity used.[2] A prime example is the use of exclusive enteral nutrition (EEN) in the management of active Crohn's disease (CD). While all patients with CD will receive the exact same treatment for the same length of time, clinical response, improvement of plasma and gut specific disease biomarkers, and mucosal healing vary considerably among patients.[3–7]

What is Known

- Diet has long been implicated in the pathogenesis of inflammatory bowel disease (IBD), although this relationship is complex and difficult to decipher.
- Epidemiology points to potentially harmful and beneficial nutrients, from a Western and Mediterranean type diets, respectively, modifying risk of development of IBD.

What is New

- There is currently no data to propose modifiers of the influence of dietary factors in increasing risk of developing IBD. The only exception is for single-nucleotide polymorphisms related to polyunsaturated fatty acid metabolism, which needs replication in independent cohorts.
- There is currently no evidence to make recommendations for precision or stratified dietary therapy for patients with established IBD. Laboratories and commercial enterprises offering such services to people with IBD should be mandated to provide the evidence base supporting their commercial services.

Such observations suggest that clinical medicine should be moving from the “one size fits all” to a stratified or individualized treatment paradigm.

Stratified or precision medicine is a novel concept of disease management where one uses patient information, a priori, to decide about the optimal treatment for this group (stratification) or individual patient (precision). A patient's prognostic information can span from disease-specific information (e.g., disease severity or phenotype) and environmental determinants of treatment response (e.g., habitual diet, exposure to sunlight), to the use of a person's omics repertoire including genetic traits, microbiome signatures and immunophenotype, or even the interactions of these parameters. In future, integration of machine learning, bioinformatics tools, and advances in systems biology may leverage opportunities to guide treatment decisions, and therefore a more personalized, efficacious, and cost-effective approach to patient care. Typical examples include thiopurine methyltransferase activity and NUDT15 polymorphisms predicting thiopurine-induced myelosuppression,[8,9] the overexpression of oncostatin M and Triggering Receptor Expressed on Myeloid cells 1 (TREM1) measured before commencing therapy predicting reduced anti-TNF agent response,[10,11] and the association of HLA-DQ1*05 genotype with immunogenicity to anti-TNF agents.[12] Likewise, studies have used microbiota signatures to predict treatment success to biologics in adult IBD, and identified pretreatment organisms associated with disease remission; hence suggesting that classification and prediction models based on microbiota may be another means for monitoring disease and treatment response.[13,14] Such models may also assist in the development and testing of more precise approaches for microbiome manipulation and might eventually lead to more effective management of CD and other forms of IBD.

As we move forward in this area of stratified and precision medicine, it is important to review the current evidence to unveil data which suggest that responses to dietary therapies in IBD can be predicted in certain groups or that the relationships between dietary factors and the risk of developing IBD depends on a person's intrinsic characteristics or environmental factors. This societal position paper aims to answer the critical question of whether we are currently in a position to predict which groups (stratified nutrition) or individual patients (precision nutrition) are less or more likely to respond to dietary therapies, or whether dietary factors interact with a person's environment and whole body biology in increasing risk of IBD development. The position paper is a joint contribution of ESPGHAN members from the ESPGHAN Special Interest Group in Basic and Translational Research, members of the IBD Porto Working Group and Allied Health Professionals; all sharing common interest in stratified and precision nutrition in IBD.

2 | METHODS

A literature search was conducted on the MEDLINE/PubMed database using the following keywords: (“inflammatory bowel disease*” OR “IBD” OR “Crohn*” OR “ulcerative colitis”) AND (“food” OR “nutri*” OR “diet*” OR “probiotic*” OR “prebiotic*” OR “synbiotic*” OR “feeds”). The search was conducted in May 2022, limited to articles published after 1990 (Figure 1). Search strategy was not limited to a specific age group, nor to specific species (e.g., humans) to mitigate the risk of excluding relevant literature. After duplicate removal, a total of 17,358 published papers were identified. This list was subsequently screened by three authors (F. G., B. T., K. G. k.) who performed a second level filtering using the title and abstract of each paper and with the help of the online tool rayyan.ai (https://www.rayyan.ai/). In this second step, case reports, letters, editorials, narrative reviews, studies performed exclusively on animal or in vitro models, errata and corrigenda, articles not fully available in English, abstracts, and communications from conferences, were excluded. Inclusion criteria were restricted to selection of original articles reporting studies conducted in humans, exclusively, or in conjunction with animal and in vitro experiments. Additional original papers were identified by screening the reference lists of systematic reviews and meta-analyses. Subsequently, eligible articles were assigned to one of the four thematic groups: (a) nutritional epidemiology for prediction of risk of developing IBD, (b) food-based dietary interventions for IBD management, (c) EEN for CD management, and (d) use pre- and probiotics for IBD management.

The assignment of papers to their respective thematic groups was performed by all three author-screeners on the first 200 entries of the 17,358 retrieved papers. Discrepancies in the selection and/or labeling were discussed to ensure that all three authors would adopt the same consistent strategy. At a final step, each of the three authors cross-checked the selection of included papers and thematic group assignment of another, and conflicts were resolved through discussion of all three authors together and when no consensus was reached with the input of the project leader (K. G.). This strategy generated a shortlist of 886 papers where at least two of the three agreed upon. Two hundred and two articles were assigned to more than one of the thematic groups. In the third and final step, the list of 886 articles was distributed across the Authors, who were split into four groups to work on each of the four thematic areas. Each author read the full text of the selected articles assigned and extracted the relevant data when appropriate. Approval from an institutional review board or ethics committee was not applicable to this review work.

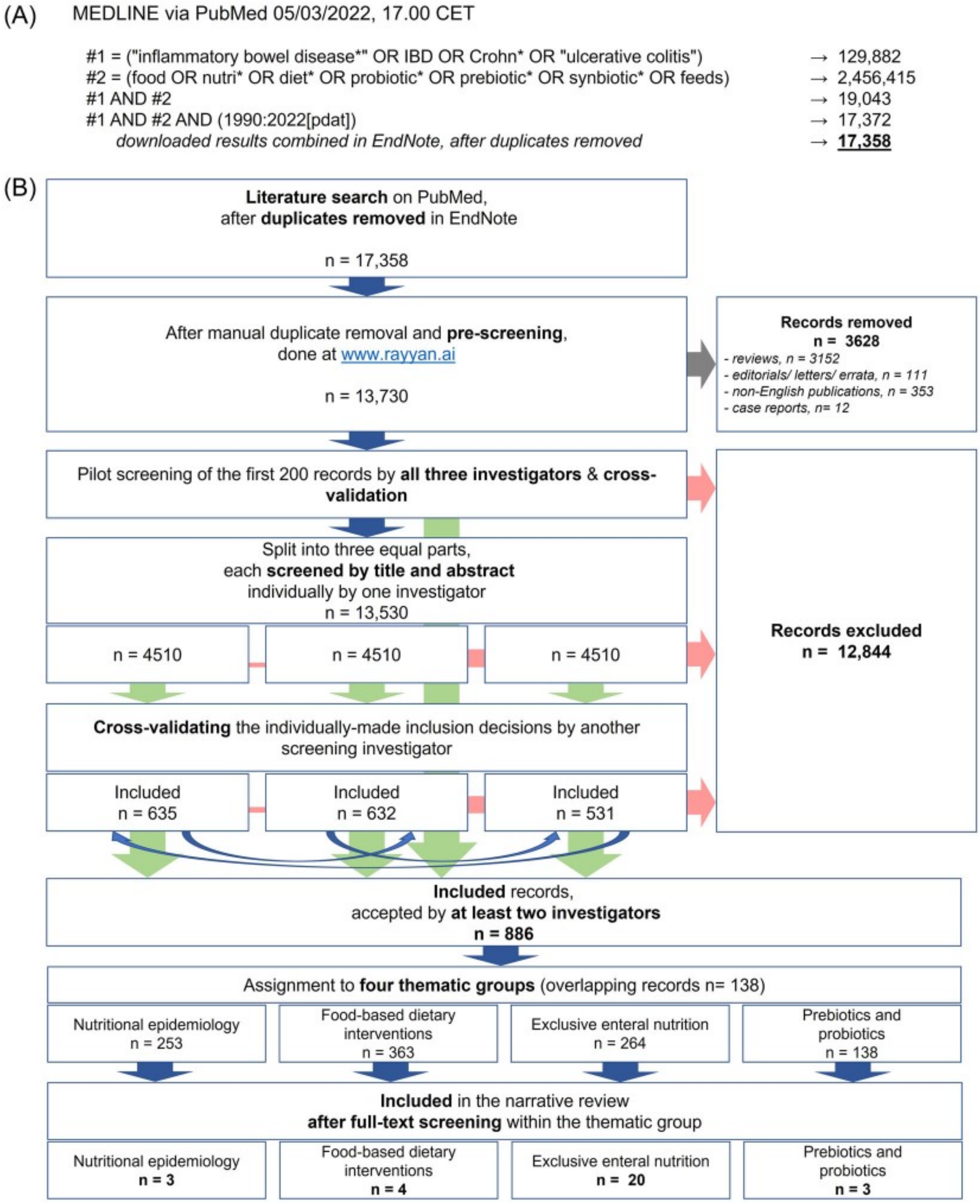

FIGURE 1 Flowchart of literature strategy search. (A) Literature search steps and (B) Cleaning and thematic categorisation of eligibile literature.

3 | NUTRITIONAL EPIDEMIOLOGY

Several environmental risk factors have been investigated with regard to development of IBD, including cigarette smoking, infections, exposure to antibiotics, breast feeding, nutritional status, and composition of diet.[15] Although results among studies are inconsistent and evidence remains inconclusive, a western-type diet with high intake of saturated fat, refined carbohydrates, red and processed meat, ultra-processed food, and low intake of fruits, vegetables, fiber, and fish is generally associated with increased risk of developing IBD.[1,15,16] Whether the relationship between a dietary component and risk of developing IBD can be modified by genetic, microbial, and other factors has been addressed by very few studies. From the 253 papers identified as potentially relevant, only three were eligible for inclusion (Table 1).

Interactions between single-nucleotide polymorphisms of pro- and anti-inflammatory cytokine genes and the type of dietary fat in modulating disease activity in CD patients were explored. A high intake of

TABLE 1 Evidence tables of nutritional epidemiological studies which explored parameters which modify the influence of dietary factors in risk of development of IBD.

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Predictor measurements	Significant results
Ananthakrishnan et al., *Inflamm Bowel Dis*, 2017	Case-control study Nested within two prospective cohorts: the Nurses' Health Study (NHS) and NHS II	101 CD 139 UC 495 controls Cases matched 1:2 to controls	Diet	Development of IBD	SNPs at CYP4F3, FADS1, and FADS2 loci	Subjects genotyped for SNPs at CYP4F3, FADS1, and FADS2 Dietary intake was assessed 4 years before diagnosis (semiquantitative FFQ)	High (above-median) intake of n–3/n–6 PUFA reduced risk of UC (OR: 0.71, 95% CI: 0.47–1.09, p 0.11) High n–3/n–6 PUFA associated reduced risk of UC in individuals with the GG/AG genotype at a SNP in CYP4F3 (OR: 0.57, 95% CI: 0.32–0.99) but not those with the AA genotype (OR: 0.95, 95% CI: 0.47–1.93; p-interaction = 0.049). No gene-diet interactions were noted for CD
Costea et al., *Gastroenterology*, 2014	Prospective case-control study	182 CD (mean age: 12.8 (3.2); females $n = 71$) 250 controls (mean age: 13.3 (3.2); females $n = 128$)	n–6/n–3 PUFA ratio	Development of CD	Genetic predisposition (SNPs)	Usual dietary consumption of PUFA 12 months before disease diagnosis using a validated FFQ 15 SNPs were investigated across three PUFA metabolic genes (FADS1, 1; FADS2, 10; and CYP4F3, 4)	Higher ratio Of LCN n–6/n–3 was associated with increased risks for CD (Q4 vs. Q1–3: OR 1.63; 95% CI: 1.01–2.64; p 0.044). None of the 15 SNPs were associated independently with CD No SNP/n6 interactions were evident, whereas interaction between 1 FADS2 SNP rs11230815 and dietary n3 was observed (p 0.042). When the dietary ratio of LCN n–6/n–3 was considered, significant interactions ($p < 0.05$) were observed involving six SNPs, suggesting that associations between the dietary ratio and CD varied according to CYP4F3 and FADS2 genotypes

TABLE 1 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Predictor measurements	Significant results
Sousa Guerreiro et al., *Am J Gastroenterol*, 2009	Retrospective, translational	99 CD (60 females; age at diagnosis 40.4 ± 14.6) 116 controls	Type of fat intake	Development of CD	Seven SNPs in interleukin 1 (IL-1), tumor necrosis factor alpha (TNF), lymphotoxin alpha (LT), and IL-6 genes	SNP detection through DNA PCR Type of fat intake was assessed through a semiquantitative FFQ	Individuals homozygous for the IL-6—174 G/C polymorphism had a sixfold higher risk for CD (OR = 6.1; 95% CI = 1.9–19.4) The TT genotype on the TNF —857 C/T polymorphism was associated with more active disease (OR = 10.4; 95% CI = 1.1–94.1). A high intake of total, saturated, and monounsaturated fats, and a higher ratio of *n*–6/*n*–3 PUFA, was associated with a more active phenotype ($p < 0.05$) A high intake of saturated and monounsaturated fats was associated with active disease, mainly in patients carrying the variant alleles of the 857 TNF_polymorphism (OR = 6.0, 95% CI: = 1.4–26.2; OR = 5.17; 95% CI = 1.4–19.2, respectively) and the 174 IL-6 polymorphism (OR = 2.95; 95% CI = 1.0–9.1; OR = 3.21; 95% CI = 1.0–10.4, respectively) Low intake of *n*–3 PUFA and high n-6/*n*–3 PUFA ratio in patients with the TNF_857 polymorphism were associated with higher disease activity (OR = 3.6; 95% CI = 1.0–13.0; OR = 5.92; 95% CI = 1.3–26.5, respectively)

Abbreviations: CD, Crohn's disease; CI, confidence interval; FFQ, food frequency questionnaire; IBD, inflammatory bowel disease; IL-1, interleukin 1; NHS, National Health System; OR, odds radio; PUFA, polyunsaturated fatty acid; SNPs, single-nucleotide polymorphisms; UC, ulcerative colitis.

saturated and monounsaturated fats, as well as a high n–6/n–3 polyunsaturated fatty acids (PUFA) ratio were associated with higher disease activity (i.e., Harvey–Bradshaw index), but mainly in patients carrying the variant alleles of the 857 TNF-α polymorphism (OR = 6.0; 95% CI = 1.4–26.2; OR = 5.17; 95% CI = 1.4–19.2; OR = 5.92; 95% CI = 1.3–26.5, respectively) and the 174 IL-6 polymorphism (OR = 2.95; 95% CI = 1.0–9.1; OR = 3.21; 95% CI = 1.0–10.4, respectively).[17] In the same study, low intake of n–3 PUFA and high n–6/n–3 PUFA ratio in patients with the TNF 857 polymorphism were associated with higher disease activity (OR = 3.6; 95% CI = 1.0–13.0; OR = 5.92; 95% CI = 1.3–26.5, respectively); hence suggesting a synergism between single-nucleotide polymorphisms and the effect of fat intake on disease activity.[17]

Ananthakrishnan et al., examined the interaction among genetic variations in enzymes involved in PUFA metabolism, dietary intake of n–3 and n–6 PUFA, and risk of disease development in women with CD and UC.[18] In UC patients, an intake of n–3/n–6 PUFA above the median, showed a trend toward reduced risk of UC (OR = 0.71, 95% CI: 0.47–1.09, $p = 0.11$). Nonetheless, high n–3/n–6 PUFA intake in the diet was associated with a reduced risk of UC in individuals with the GG/AG genotype at a single-nucleotide polymorphism in CYP4F3 (OR: 0.57, 95% CI: 0.32–0.99), involved in dampening proinflammatory response via its ability to inactivate leukotriene B4, but not those with the AA genotype (OR: 0.95, 95% CI: 0.47–1.93).[18] In the same study, no interactions between diet with genetic markers were identified for CD. Likewise, in a case-control study, children with CD with a higher dietary ratio of n–6/n–3 were susceptible to CD if they were also carriers of specific variants of the CYP4F3 and FADS2 genes involved in PUFA metabolism.[19] Collectively, these studies suggest the possibility of a PUFA metabolic status that facilitates chronic inflammation in response to dietary intake of these fatty acids; however, independent replication is required and confirmation of causality of these observations within intervention studies is also needed.

4 | EEN

EEN is the primary induction treatment for children with mild to moderate luminal CD.[20] Treatment with EEN results in high rates of clinical response and remission and is paralleled by biochemical remission too, but in a smaller proportion of patients.[21] Its near absent side effect profile supported by its ability to promote mucosal healing and "reverse" stenosis in some patients, as well as providing parallel nutritional rehabilitation, make it an attractive treatment option. Major barriers in the use of EEN include the monotony of the dietary regime with taste fatigue, increased social isolation, and the frequent need for tube feeding; hence the significant commitment and resource needed to support its use.[22] Therefore, EEN would be best tailored to patients for whom an effective outcome could be predicted before or shortly after commencing its use. Studies which explored elements of EEN treatment stratification or precision are summarized in Table 2. From the 264 papers identified as potentially relevant, only 20 were deemed eligible for inclusion.

4.1 | Clinical and laboratory parameters

The "simplest" way to predict response to EEN and stratify treatment, is to use clinical parameters. Disease phenotype has been analyzed by several research groups. Inflammatory disease behavior (Paris B1)[23] rather than complex (fibrostenotic or penetrating; B2/B3) disease behavior has a more favorable response profile.[24,25] In contrast, colonic disease[24,26,27] and the presence of perianal disease are both associated with a lower rate of EEN response.[28,29] Small bowel disease, particularly disease affecting the ileum[6,30,31] has been associated with better response than isolated colonic, but in contrast, disease in the proximal small bowel has been associated with worse outcomes.[26] The data are however inconsistent with some of the differences possibly explained by varying phenotype definitions and sample size.[31–33] While EEN treatment courses of different length are used clinically (2–12 weeks), an EEN course of more than 6 weeks has been shown to be more successful than shorter courses.[34] Younger age, in children, and lower lean body mass at baseline, have both been linked to improved outcomes.[26,27,35]

Clinical markers have also been used as predictors of EEN efficacy. Normal albumin levels at baseline and reduction of fecal calprotectin halfway through an EEN course,[4,26] both as absolute value and degree of change from baseline, have been proposed as predictors of response. A subsequent study showed association of both with clinical remission at EEN completion but with lower accuracy.[36] In a Spanish-wide study, children with CD with a weighed pediatric CD activity index ≤57.5, fecal calprotectin <500 µg/g, CRP > 15 mg/L, and ileal involvement, tended to respond better to EEN.[30] Likewise, an Italian study in children with CD found that a lower PCDAI, younger age and male gender, at the point of treatment, were predictors of EEN response.[33] In a recent study in China, the simple endoscopic score for CD was negatively associated with mucosal healing at EEN completion (OR = 1.40 95% CI = 1.12–1.67, $p < 0.001$) and at 1-year post-EEN follow-up (OR = 1.33, 95% CI = 1.12–1.58, $p = 0.001$). The authors recommended that children with CD with a simple endoscopic score for CD cut-off value > 11.5 should be treated with biologics.[37]

TABLE 2 Evidence tables of studies which explored aspects of treatment precision/stratification in patients with Crohn's disease on exclusive enteral nutrition.

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Significant results
Kakkadasam Ramaswamy, et al., *JPEN*, 2022	Retrospective	$N = 39$ adults	8-week EEN	Primary endpoint: remission (CDAI ≤ 150) or response (CDAI decrease >100). Secondary endpoint: CRP ≤ 5 mg/L or FCAL ≤ 150 mg/kg	EEN duration, disease location and behavior, CRP, FCAL, Alb, Weight, Vit D3, Use of biologics	Patients with EEN ≥ 6 weeks had higher primary endpoint rates (72% vs. 47.8%), $p = 0.047$ and secondary endpoint rates (67.6% vs. 36.8%), $p = 0.035$; versus patients on EEN < 6 weeks EEN ≥ 6 weeks was the only significant predictor of achieving remission/response; OR (95% CI): 2.8 (0.97–8.16), $p = 0.047$; or SE: 3.58 (1.1–11.6), $p = 0.035$. In multivariate model, association with SE remained significant ($p = 0.043$)
Tang et al. *Front Pediatr.*, 2022	Retrospective	$N = 50$ children, Female: $N = 17$	≥6-week EEN, ≥12-month follow-up	Mucosal healing at end of EEN (SES-CD < 3) SES-CD at 1 year; SES-CD < 3: sustained mucosal healing (sMH) versus SES-CD ≥ 3: sustained non-MH (sNMH)	Age, gender, disease duration, SES-CD, Lewis score, wPCDAI, FCAL, Hgb, Alb, ESR, disease location	End of EEN analysis: In univariate regression analysis: SES-CD, ESR, and presence of B2/B3 classification positively associated whereas Alb and Hgb negatively associated with SES-CD at end of EEN. In multivariate model, only SES-CD remained significant; OR (95% CI): 1.40 (1.12–1.67), $p < 0.001$ 1-year follow-up analysis: Lower SES-CD at baseline in sMH (8.7 ± 1.2) versus sNMH (16.2 ± 1.0), $p < 0.001$ Lower wPCDAI at baseline in sMH (37.1 ± 3.1) versus sNMH (47.1 ± 2.9), $p = 0.04$ Lower ESR at baseline in sMH (46.1 ± 9.1) versus sNMH (67.9 ± 4.8), $p = 0.02$ Higher Alb at baseline in sMH (40.2 ± 1.2) vesus sNMH (35.1 ± 1.1), $p < 0.01$ More patients with baseline L1 location in sMH: 8 (47%) versus sNMH: 1 (3%), $p < 0.001$ and fewer patients with baseline L3 location in sMH: 8 (47%) versus sNMH: 27 (82%), $p = 0.02$ Fewer patients with baseline B2/B3 classification in sMH: 0 (0%) versus sNMH: 9 (7%), $p = 0.02$ Like end of EEN, only baseline SES-CD was a significant predictor of SES-CD at 1-year post EEN in a multivariate model: 1.33 (1.12–1.58), $p = 0.001$ ROC analysis showed that optimal cutoff value of SES-CD (11.5) at baseline predicted MH at end of EEN with AUC = 0.91 and 1-year follow-up with AUC = 0.83 (both $p < 0.001$)

(Continues)

TABLE 2 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Significant results
Tang et al., *JPEN*, 2021	Prospective	$N = 31$ children Male: $N = 18$	8-week EEN	Mucosal healing: Response: SES-CD ≤ 4 versus nonresponse: SES-CD > 4	At 2 weeks of EEN; Shannon diversity wPCDAI Hgb, Alb Weight gain	Lower wPCDAI at Week 2 of EEN in responders (11.2 ± 2.12) versus nonresponders (28.8 ± 7.69), $p = 0.01$. Higher Shannon diversity index scores in responders (2.34 ± 0.16) versus nonresponders (1.68 ± 0.23), $p = 0.02$ Baseline wPCDAI and Shannon index did not differ between the two groups
Diederen et al., *Sci Rep*, 2020	Prospective	$N = 43$ Male: 47%, Age, median (IQR): 14 (12–15)	6-week EEN	FCAL response: decrease in FCAL of ≥50%	Fecal microbiome (16S sequencing); α -diversity (Shannon, inverse Simson diversity indices), B-diversity (Bray–Curtis dissimilarity), Individual taxa Fecal metabolome (NMR) Fecal amino and bile acids (HPLC)	B-diversity different between responders versus nonresponders at baseline ($p = 0.008$) Taxa higher in nonresponders: *Dorea longicatena* ($p = 0.012$), *Blautia obeum* ($p = 0.019$), *Bifidobacterium longum* ($p = 0.04$) No differences in α-diversity Fecal metabolic profile different between responders versus nonresponders at baseline ($R^2 = 60.4\%$, $Q^2 = 0.28$, $p = 0.030$); ROC curve (AUC = 0.8) of metabolic profile able to predict EEN response at baseline No significant differences in amino acid and bile acid profiles between responders versus nonresponders
Abdalla et al., *Colorectal Dis*, 2020	Retrospective	$N = 149$ adults; Male: $N = 68$, Age, mean ± SD: 34.7 ± 13.1 year	Preoperative EEN for up to 2 weeks before surgery	Failure of EEN (need for parenteral nutrition)	Disease behavior	Patients with perforating CD and preoperative intestinal fistula had higher risk of EEN failure EEN failure in perforating: 15/40 (38%) versus nonperforating: 5/31 (16%), $p = 0.047$ EEN failure in preoperative intestinal fistula: 14/31 (45%) versus no fistula: 6/37 (16%), $p = 0.02$
Moriczi et al., *Nutrients*, 2020	Retrospective	$N = 222$ children Male: $N = 130$ Age (mean ± SD): 11.6 ± 2.5	EEN; median (IQR) duration: 8 weeks (6.7–8.5)	Clinical remission: wPCDAI <12.5	Age Disease location (Paris classification) wPCDAI CRP, FCAL	EEN responders had lower PCDAI ($p = 0.011$) and FCAL ($p = 0.011$) versus nonresponders at baseline Multivariate regression model OR (95% CI) including wPCDAI ≤ 57.5: 3.8 (1.5–9.7), $p = 0.005$; FCAL < 500 mg/kg: 6.9 (1.3–35.4), $p = 0.019$; CRP > 15 mg/L: 2.6 (1.01–6.8), $p = 0.047$; Ileal involvement: 6.3 (1.09–36.6), $p = 0.039$ associated with better response to EEN
Hart et al., *Nutrients*, 2020	Prospective	$N = 16$ children Male: $N = 11$ Age range: 5 = 18 year	8-week EEN	Clinical remission: PCDAI ≤ 10	Shannon diversity index at Week 2	Patients achieving clinical remission had higher Shannon diversity at Week 2 of EEN ($p = 0.044$) versus those not achieving remission

TABLE 2 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Significant results
Jones et al., *Inflamm Bowel Dis*, 2020	Prospective	$N = 22$ children	EEN for at least 12 weeks	Sustained remission at Week 24 (wPCDAI ≤12.5)	Fecal microbiome composition (16S sequencing); α-diversity, individual taxa Fecal microbiome functionality; metabolic pathways and KEGG orthologs	Lower α-diversity in sustained remission group versus non-sustained remission group at baseline (p value not available) Trend for higher Proteobacteria levels in non-sustained remission group at baseline versus sustained remission (p value not significant) Random forest model showed that only microbiome variable significantly predicting sustained remission with EEN was ASVs ($p = 0.047$) Addition of species richness, disease location, and behavior to an ASV RF model improved the accuracy of the model from AUC = 0.743 to AUC = 0.9 Most important variables: *Ruminococcaceae UCG-002, Lachnospiraceae NK4A136, Bacteroides, and Parabacteroides*
Xu et al., *Clin Nutr*, 2019	Retrospective	$N = 241$ adults, Male: $N = 158$ Age, mean ± SD: 36.2 ± 12.5 year	No less than 2 weeks of EEN; mean duration: 26.5 days	Clinical remission: CRP < 10 mg/L and HBI ≤ 4 EEN failure: 1. HBI > 4 and/or CRP > 10 mg/L 2. New induction treatment 3. Noncompliance	Sex, age BMI New diagnosis Disease location and behavior Smoking Medication CRP, Alb, ESR, LBMI	Clinical remission rates lower in patients with colonic disease location 52% versus non-colonic: 68%, $p = 0.029$ Isolated colonic disease (OR [95% CI]: 2.74 [1.2–6.23], $p = 0.016$) and baseline CRP (OR [95% CI]: 1.01 [1.003–1.017], $p = 0.008$) were independent risk factors for EEN failure LBMI negatively associated with EEN failure: OR (95% CI): 0.636 0.444–0.912), $p = 0.014$)
Xu et al., *Therap Adv Gastroenterol*, 2019	Retrospective	$N = 85$ adults with isolated colonic CD Female: $N = 37$ Age, mean ± SD: 33.0 ± 13.2 year	No less than 2 weeks of EEN	Clinical remission: CRP < 10 mg/L AND HBI ≤ 4 EEN failure: 1. HBI > 4 and/or CRP > 10 mg/L 2. New induction treatment 3. Noncompliance	Sex, age Smoking Medication BMI Disease location and behavior SES-CD LBMI CRP, ESR, Alb	Pancolitis was the greatest contributor to risk of EEN failure; OR (95% CI): 4.89 (1.22–19.6); $p = 0.025$. Colonic lesion features (stricturing): (2.32 [1.14–4.71], $p = 0.02$), SES-CD (1.89 [1.09–4.12], $p = 0.014$), baseline CRP (1.01 [1.01–1.03], $p = .041$) positively associated with EEN failure LBMI (0.377 [0.206–0.689], $p = 0.002$) and albumin change 1-week post-EEN (0.983 [0.972–0.995], $p = 0.005$) negatively associated with EEN failure
Copova et al., *Eur J Pediatr*, 2018	Prospective	$N = 38$, Male: $N = 28$, Age: median (IQR): 12.8 (9.7–15.5)	6-week EEN	Clinical response: wPCDAI ≤12.5 or drop in wPCDAI >17.5 Clinical remission: wPCDAI ≤12.5	Change in FCAL from baseline to Week 2	Change in FCAL not a significant predictor of lack of clinical response to EEN; OR (95% CI) 0.99 (0.99–1.00), $p = 0.08$ Change in FCAL significantly associated with clinical remission; OR (95% CI): 0.99 (0.99–0.99), $p = 0.006$

(Continues)

TABLE 2 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Significant results
						Best cut-off: increase in FCAL by 486 mg/kg, AUC: 0.753, sensitivity: 58%, specificity: 92%
Cuomo et al., *Inflamm Bowel Dis*, 2017.	Retrospective	$N = 376$ children Male = 241 Age, median (IQR): 13 (10–14)	8-week EEN	Clinical remission: PCDAI ≤ 10	Sex, age Disease location (Paris classification) PCDAI CRP, ESR, albumin Hgb, Hematocrit, Iron FCAL	Male gender and lower PCDAI at baseline associated with increased EEN efficacy. Male gender; *n* (%); responders: 170 (67%) versus nonresponders: 43 (54%), $p = 0.036$ PCDAI baseline; median (IQR); responders: 30 (20–37.5) versus nonresponders: 35 (25–40), $p = 0.002$ Age and PCDAI independent predictors of remission; age, OR (95% CI): 1.10 (1–1.21), $p = 0.049$, PCDAI: 1.04 (1.01–1.06), $p = 0.001$
Dunn et al., *Inflamm Bowel Dis*, 2016	Prospective	$N = 10$ children Female: $N = 3$ Age range: 10–16 year	12-week EEN	Sustained clinical remission at Week 24: wPCDAI <12.5	Fecal microbiome (16S sequencing); α-diversity (Chao index), individual taxa	Higher α-diversity in sustained remission group versus non-sustained remission group observed throughout the 24-week period (no *p* value) Higher Proteobacteria in sustained remission group versus non-sustained remission group (no *p* value) Using fecal microbiome data, a Bayesian model was able to correctly predict response to EEN in 15/19 fecal samples Most important contributors to sustained remission group: Bacteroidetes, Firmicutes, Verrucomicrobia, Akkermansia muciniphila, Bacteroides, Lachnospiraceae, and Ruminococcaceae Most important contributors to non-sustained remission group: Bacteroidetes, Proteobacteria, *Bacteroides* Enterobacteriaceae, *Prevotella*
Kim et al., *Yonsei Med J*, 2016	Retrospective	$N = 66$ children, Female = 12 Age (range): 13 (10–17) year	6-week EEN	Clinical remission: PCDAI < 10	Disease behavior (Paris classification)	Higher clinical remission rates in patients with inflammatory disease behavior (B1): 93% versus patients with stricturing disease behavior (B2) 63% ($p = 0.033$)
Konno et al., *Pediatr Int*, 2015	Retrospective	$N = 58$ children, Female: $N = 23$ Age, mean ± SD: 11.9 ± 2.7 year	MEN: EN (30 kcal/kg/day) after induction with EEN/TPN	Continuous clinical remission: PCDAI < 10 and SES-CD score <2	Disease location, disease behavior	Lower remission rates in patients with penetrating disease behavior (B3) versus patients with inflammatory (B1); HR (95% CI): 0.2, (0.1–0.6), $p = 0.044$ and stricturing behavior (B2), ($p = 0.023$). Higher surgery rates in patients with L1 disease location versus L3 ($p = 0.014$) and in patients with B2 disease behavior versus B1 ($p = 0.015$)

TABLE 2 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/ exposure	Outcome measurements	Predictors assessed	Significant results
Frivolt et al., *Aliment Pharmacol Ther*, 2014	Retrospective	$N = 52$, Male = 31, Age, mean ± SD: 12.6 ± 3.2 year	6–8 week-EEN	Clinical relapse: wPCDAI ≥12.5	Age Disease location EEN duration Systemic inflammatory markers NOD2 genotype	Lower clinical relapse rates in patients with wild-type 12/20 (60%) or 1007fs (6/12) (50%) mutations compared to those with the R702W or G908R genotype11/12 (92%) ($p < 0.01$) Younger age at baseline negatively associated with time to clinical relapse ($r = -0.31$, $p < 0.05$)
De Bie et al., *J Crohns Colitis*, 2013	Retrospective	$N = 77$ children, Male: 57%, Age, median (IQR): 13.9 (11.1–15.7)	6-week EEN	Complete remission: ≤2 stools/day, no blood, pus, or mucus, no abdominal pain, stable weight Partial remission: ≤4 stools/day, less than daily loss of blood, pus, or mucus with stools, less than abdominal pain, or weight loss	Disease location (Paris classification) Anthropometry (BMI for age)	Higher complete remission rates in patients with L1 ($n = 14/40$, 35%) versus L2 ($N = 8/40$, 20%) and L3 ($n = 18/40$, 45%), $p = 0.04$ Higher BMI for age (median [IQR]) in patients with complete remission (−1.6 [−2.2 to −0.75]) versus those with partial/no response (−0.24 [−1.4 to 0.69]), $p < 0.001$ In multivariate logistic regression, disease location and nutritional status remained significant predictors of remission
Tjellström et al., *Scand J Gastroenterol*, 2012	Retrospective	$N = 18$ children, Female: $N = 7$, Age, median (range): 13.5 (10–17) year	6-week EEN	Clinical remission: PCDAI < 10	Presence of perianal disease	None of the children with perianal disease responded to EEN
Gerasimidis et al., *J Clin Gastroenterol*, 2011	Observational	$N = 15$ children, Female = 7, Age, mean ± SD: 11.6 ± 2.3 year	8-week EEN	Clinical remission: PCDAI ≤ 10	FCAL	No difference in baseline FCAL levels between responders versus nonresponders At Day 30 of EEN, FCAL levels ($p = 0.005$) and % change lower ($p = 0.002$) in responders versus nonresponders
Borrelli et al., *Clin Gastroenterol Hepatol*, 2006	RCT	$N = 37$, $N = 19$: EEN, $N = 18$: corticosteroids, EEN: Age, median (range): 11 (4–16) year, female = 12	10-week EEN	Endoscopic response; disappearance of ulcerative lesions	Disease location	Endoscopic response in ileal disease location: 13/15 (87%) versus endoscopic response in colonic disease location: 9/12 (75%)
Esaki et al.	Retrospective	$N = 145$, adults and children, Female: $N = 37$	MEN (EN > 1200 kcal/day) as	Disease flare: CDAI > 150 and CDAI increase of >70 from baseline	Disease location and behavior, history of surgery	Penetrating disease behavior, colonic location, and previous surgery were independent risk factors of disease flare in MEN group

(Continues)

TABLE 2 (Continued)

Author, journal, publication year	Study design	Subjects	Intervention/exposure	Outcome measurements	Predictors assessed	Significant results
Dis Colon Rectum, 2006		Age range: 11–62 year	maintenance, follow-up: 3–232 months			Penetrating behavior; RR (95% CI): 3.89 (1.58–9.62), $p = 0.003$ Colonic involvement: 3.1 (1.39–6.9), $p = 0.006$ Previous surgery: 2.48 (1.16–5.33), $p = 0.02$
Afzal et al., *Dig Dis Sci*, 2005	Prospective	$N = 65$ children, Male: $N = 45$, median age: 13.6	8-week EEN	Clinical remission: PCDAI < 20	Disease location	Lower clinical remission rates in patients with colonic disease ($n = 7/14$, 50%), versus ileal ($n = 11/14$, 92%) and ileocolonic ($n = 32/39$, 82%) ($p = 0.021$)

Abbreviations: Alb, albumin; AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; CRP, C-reactive protein; EEN, exclusive enteral nutrition; EN, enteral nutrition; ESR, erythrocyte sedimentation rate; FCAL, fecal calprotectin; HBI, Harvey–Bradshaw index; Hgb, hemoglobin; HPLC, high performance liquid chromatography; HR, hazard ratio; IQR, interquartile range; LBMI, lean body mass index; MEN, maintenance enteral nutrition; NMR, nuclear magnetic resonance; OR, odds radio; PCDAI, pediatric Crohn's disease activity index; RF, random forest; RR, relative risk; SES, simple endoscopic score; TPN, total parenteral nutrition; wPCDAI, weighted PCDAI.

4.2 | Microbiome

The interaction of EEN and the microbiome has been widely studied[38–40] (Table 2). A change in microbial α diversity (measured by Shannon index) has been linked with response to EEN in two studies. In the study by Hart et al., patients who were in remission at EEN completion (Week 8) had a significantly higher Shannon diversity score at Week 2 compared to nonresponders.[40] This finding was replicated by Tang et al. at the same time points with no effect noted from diversity at baseline.[41] Another study suggested that baseline microbial community structure (β diversity, Bray–Curtis dissimilarity) and the fecal metabolomic profile of patients, assessed by NMR, but not α-diversity were linked to EEN response.[42] Bacterial organisms identified as predictors of nonresponse to EEN included *Dorea longicatena*, *Blautia obeum*, and *Bifidobacterium longum*.[42] Two small studies from the same groups found that pretreatment microbiome signatures were associated with sustained clinical remission at 12 weeks after completion of EEN treatment.[43,44] A composite index of abundance, richness and disease location was found to be the best predictor of response to EEN.[43]

4.3 | Genetic markers

Frivolt et al., demonstrated significant differences in relapse rates up to 12 months after a 6–8 week course of EEN, based on analysis of the three common mutations in the NOD2/CARD15 CD susceptibility gene.[35] In 48 patients with a 91% response rate to EEN, mutations did not predict response to EEN itself, only relapse rate up to a year. Those carrying the genotype R702W or G908R had a 92% relapse by a year compared to a lower relapse in those with 1007fs mutation or none of the three common mutations at all (60% and 50%, respectively). The 1007fs mutation is strongly associated with the presence of ileal disease which may add some biological plausibility to the finding although the numbers of patients were small and without replication this is a finding of unknown significance.

5 | FOOD-BASED DIETARY THERAPIES

Over the past four decades, there have been several attempts to develop new dietary therapies to induce and maintain disease remission. A recent literature review in 2021 identified 24 different dietary therapies proposed for the management of IBD,[1] with at least three more therapies proposed since then. Most of the studies reported summary data regarding response to treatment assessed either with disease activity indices, disease biomarkers or endoscopic findings.[1] There is currently no consensus or consistent data to favor one dietary regimen over another; perhaps with the exception for the CD exclusion diet coupled with 50% partial enteral nutrition (PEN) and daily intake of five mandatory food (CDED&PEN).[45] This dietary regime aims to improve gut inflammation in patients with CD by minimizing the intake of dietary components which cause dysbiosis and negatively impact intestinal immunity. Data from two retrospective studies from the same research group demonstrated that the efficacy of CDED&PEN might be dependent on baseline disease severity.[46,47] In their first study, the baseline PCDAI (without height) scores were significantly lower in children with CD who achieved clinical remission following a 6-week CDED&PEN course, compared to those who failed to achieve remission (PCDAI, mean ± SD; clinical remission: 26.1 ± 9 vs. no remission: 32 ± 9, $p = 0.013$).[47] In their second study, CDED&PEN was not effective in treating patients who lost response to biologics and presented with severe CD (HBI ≥ 13) at study enrollment.[46] Patients achieving remission at Week 3 of their course were more likely to achieve remission at week 6 (OR: 6.37, 95% CI: 1.6–25, $p = 0.008$), after multivariable analysis.

Certain individuals develop IgG antibodies to specific food consumption, the significance of which remains unclear. In an RCT, CD patients who followed a diet which excluded food in which they presented an elevated IgG4 response showed a more favorable change in CD activity index and quality of life scores, but no difference in objective laboratory biomarkers (e.g., fecal calprotectin and CRP) than those who followed a sham diet.[48] Similar findings were reported by another study in China.[49]

For the remaining dietary therapies reported in the literature, predictors of treatment effectiveness were not explored. This may represent a level of uncertainty on the effectiveness of these dietary therapies, but also the fact that it is difficult to discern treatment failure from noneffective treatment, or poor adherence to the diet, particularly in broad exclusion dietary therapies where dietary intake and food diversity are variable between and within participants. We have not identified any published studies which aimed to deliver a certain dietary regime tailored upon the microbial signatures of host immunophenotype, genetic markers, or disease characteristics.

6 | PREBIOTICS & PROBIOTICS

The human gut microbiota is composed of thousand different organisms with a large functional diversity that surpasses the human gene pool.[50] Like other noncommunicable diseases, the gut microbiota has been implicated in the underlying etiology of IBD.[51] Reproducible evidence shows that the gut microbiota in patients with IBD presented a loss of functional and taxonomic diversity, enrichment of putative pathogens and pathobionts, and a parallel depletion of health-promoting species, including fiber-fermenting bacteria.[51] Upon these observations, previous and current research aimed to improve disease outcomes in all age IBD using microbiota modifying treatments like probiotics and prebiotics.

Overall, the data are negative and there is no supportive evidence on the use of either probiotics[52] or prebiotics in the management or active CD or CD in remission. In patients with UC, data are inconsistent for prebiotics.[53] Low-certainty evidence suggests that certain probiotics (*Escherichia coli* Nissle 1917) may induce clinical remission in active UC when compared to placebo.[54]

There are very few studies published on the use of prebiotics/probiotics and predictors of effectiveness in IBD, and in those studies which did so, no significant interactions were observed. For example, *Lactobacillus johnsonii* LA1 failed to significantly reduce risk of endoscopic recurrence 6-months after surgery for CD, and treatment effect was not modified when adjusted for smoking habit, CRP level and type of resection.[55] This was also the case in another study where use of *Saccharomyces boulardii* failed to prolong CD remission in steroid or salicylate induced remission; albeit nonsmokers given *S. boulardii* were less likely to experience a relapse of CD than nonsmokers given placebo.[56] Valcheva et al. assessed the effect of supplementation with two different doses of an oligofructose-enriched inulin supplement (7.5 and 15 g) on markers of disease activity in patients with UC. Neither baseline microbiota composition nor baseline SCFA levels could successfully predict response to treatment.[57]

7 | CONCLUSIONS

Considering the currently (limited) available literature presented within this manuscript (Figure 2), we conclude that:

- There is currently no robust data to propose modifiers of the influence of dietary factors in increasing risk of developing IBD. The only exception is for single-nucleotide polymorphism related to PUFA metabolism; findings of which still need replication in independent groups.
- There is currently no evidence to make recommendations for precision or stratified dietary therapy for patients with established IBD. Laboratories and commercial enterprises offering such services to

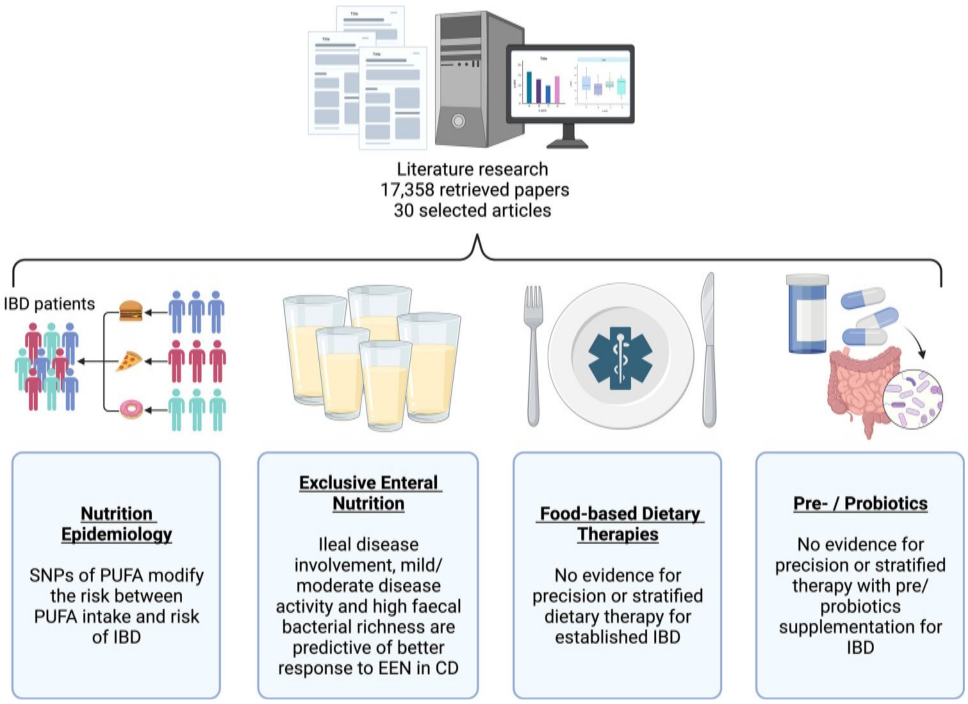

FIGURE 2 Summary of available literature on implications for precision and stratified nutrition and dietary therapy in inflammatory bowel disease. EEN, exclusive enteral nutrition; IBD, inflammatory bowel disease; PUFA, polyunsaturated fatty acid.

people with IBD are mandated to provide the evidence base supporting their commercial services.

- Disease factors (e.g., ileal disease involvement), mild/moderate disease activity, and microbial signatures (e.g., high bacterial richness) may be used to predict success of EEN, but also for early cessation in nonresponders. Confirmation of these findings in independent research, in clinical practice setting and within RCTs is required.

8 | FUTURE RESEARCH

In evolving the field of stratified and precision nutrition in IBD, it is of crucial importance that we first unravel the complex interaction of food causing and treating IBD. Only then, it will be possible to distinguish between responders and nonresponders to a certain dietary therapy. In addition to this, future research should leverage existing ‘omics technologies, system biology and artificial intelligence to unravel the complex relationships between host genetics, biology, immunophenotype, and gut microbiome with response to a dietary therapy. For the latter to happen, it is important we move away from subjective clinical disease scores, which are inherent to placebo effect and assessor bias, to more objective disease biomarkers which better reflect inflammatory activity in the lumen (e.g., fecal calprotectin) or endoscopy and novel composite indices.[58] The imperative is to prospectively collect appropriate dietary intake information, not just using conventional dietary assessment methodology but also supported by novel more objective biomarkers of food intake and dietary adherence,[59,60] to build these associations. Typical examples include the detection of gluten immunogenic peptide in feces as a marker of compliance to gluten free dietary therapies, including EEN,[59] measurement of PUFA in erythrocyte membranes to indicate medium/long-term intake of these fatty acids,[61] or even measurements of micronutrients in blood which may be better biomarkers to indicate body levels than dietary assessment[62,63] and novel ‘omics based technologies coupled with artificial intelligence.[64] Hypotheses generated within such research need further confirmation within independent studies and within RCT, where identified predictors are modified before treatment initiation and treatment effectiveness is monitored and compared between groups; hence establishing causal associations. A prime example might be preconditioning or preoptimization of gut microbiome before EEN initiation using microbial therapeutics like antibiotics, prebiotics, or certain diets. Easy to measure clinical or modifiable parameters are likely to be the most translatable into clinical practice and for bedside use, than complex multiomics technologies. The advantage new biomarkers have to offer against routine biomarkers and disease characteristics is important to justify. Alternatively, wearable devices with passive data acquisition and monitoring, or home biomarker testing may help to identify individual responses to food and provide an alternative avenue to precision nutrition.[65]

In conclusion, while there is a great interest to stratified and precision nutrition from patients, their healthcare providers, and commercial enterprises, we currently lack data to make any such recommendations.

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CONFLICT OF INTEREST STATEMENT

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