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## ARTICLE TITLE

THE ROLE OF MICROBIAL ENGRAFTMENT AND KEYSTONE SPECIES IN THE EFFICACY OF FAECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE - A REVIEW OF RECENT STUDIES

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# THE ROLE OF MICROBIAL ENGRAFTMENT AND KEYSTONE SPECIES IN THE EFFICACY OF FAECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE - A REVIEW OF RECENT STUDIES

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## ABSTRACT

**Background:** Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, are chronic relapsing disorders in which alterations of the gut microbiota contribute to disease pathogenesis. Despite advances in pharmacological therapies, sustained remission remains difficult to achieve in many patients, prompting interest in microbiome-targeted interventions such as faecal microbiota transplantation.

**Objectives:** This study aimed to review evidence published between 2015 and 2025 on the efficacy of faecal microbiota transplantation in inflammatory bowel diseases, with emphasis on donor microbiota engraftment, keystone taxa, the donor effect, and differences between ulcerative colitis and Crohn's disease.

**Methods:** A narrative–systematic review of clinical, metagenomic, and ecological studies addressing faecal microbiota transplantation in inflammatory bowel diseases was conducted using major biomedical databases.

**Results:** Clinical response following faecal microbiota transplantation was more consistently associated with stable and functional engraftment of donor-derived microbial strains than with restoration of microbial diversity alone. Evidence supporting this association was stronger in ulcerative colitis, whereas data in Crohn's disease remained limited and largely observational. Variability in outcomes appeared to reflect interactions between donor and recipient microbiota.

**Conclusions:** Faecal microbiota transplantation represents a complex ecological intervention, the efficacy of which depends on engraftment stability, functional reconstruction of the gut microbiome, and recipient-specific ecological context.

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## KEYWORDS

Faecal Microbiota Transplantation, Inflammatory Bowel Disease, Microbial Engraftment, Keystone Taxa, Donor Effect, Gut Microbiome

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## Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing disorders characterized by a complex and heterogeneous pathogenesis. Despite significant advances in immunomodulatory and biologic therapies, a substantial proportion of patients fail to achieve sustained remission or experience disease relapse, highlighting the need for complementary therapeutic strategies targeting additional components of IBD pathogenesis (Aldars-Garcia, Chaparro, & Gisbert, 2021; Halfvarson et al., 2017; Lloyd-Price et al., 2019; Morgan et al., 2012; Ni, Wu, Albenberg, & Tomov, 2017).

One of the key factors involved in the development and course of IBD is disruption of the gut microbiota. Metagenomic studies and multi-omics analyses have demonstrated that both UC and CD are characterized by profound dysbiosis, encompassing not only reduced microbial diversity but also functional alterations in short-chain fatty acid metabolism, secondary metabolite synthesis, and reorganization of microbial interaction networks (Aldars-García et al., 2021; Franzosa et al., 2019; Gevers et al., 2014; Halfvarson et al., 2017; Imhann et al., 2018; Lloyd-Price et al., 2019; Ni et al., 2017; Pascal et al., 2017). Importantly, the nature and depth of these disturbances differ between UC and CD, suggesting distinct ecological properties of the gut ecosystem in these two disease phenotypes (Gevers et al., 2014; Imhann et al., 2018; Lloyd-Price et al., 2019; Pascal et al., 2017).

In light of the growing recognition of the role of the gut microbiome in IBD pathogenesis, therapeutic strategies aimed at microbiome modulation have been intensively investigated. Faecal microbiota transplantation (FMT), originally applied with high efficacy in the treatment of recurrent *Clostridioides difficile* infection, has been proposed as a potential therapeutic option in IBD (Bi, Cheng, Zou, Liu, & Cui, 2025; Fanizzi et al., 2024; Ishikawa, Zhang, Nomura, & Nagahara, 2025; Nowak et al., 2022; Sunkara, Rawla, Ofosu, & Gaduputi, 2018). Meta-analyses and randomized clinical trials have demonstrated that FMT may induce clinical remission in a subset of patients with active UC, whereas its efficacy in CD remains less

consistent and more variable (Caldeira et al., 2020; Feng et al., 2023; Imdad et al., 2018; Liu, Li, Yuan, Huang, & Xu, 2023; Paramsothy et al., 2017). At the same time, clinical studies indicate substantial heterogeneity in response to FMT, even when similar therapeutic protocols are applied (Caldeira et al., 2020; Fanizzi et al., 2024; Imdad et al., 2018).

The efficacy of FMT depends, among other factors, on the treatment regimen, route of administration, number of transplantations (Singhal et al., 2025), as well as on characteristics of the donor microbiota that influence post-transplant microbiome dynamics and durability of response (Paramsothy et al., 2017; Pinto et al., 2025; Steube, Stallhofer, & Stallmach, 2023). Reports addressing the safety of FMT further indicate that manipulation of the gut microbiome is not biologically neutral, and that observed adverse events—although generally mild to moderate in severity—highlight the importance of a better understanding of the mechanisms determining both the efficacy and durability of therapeutic effects (Patryn et al., 2024). These observations suggest that FMT should not be regarded as a simple “microbiota replacement”, but rather as a complex intervention within the recipient’s pre-existing gut ecosystem (Caldeira et al., 2020; Fanizzi et al., 2024; Ianiro et al., 2022; Ishikawa et al., 2025).

Increasing attention has therefore been directed toward the process of engraftment, defined as the stable and functional colonization of donor-derived strains within the recipient’s gut. Clinical and metagenomic data indicate that stable engraftment more frequently accompanies clinical response, particularly in UC; however, colonization alone is not sufficient to achieve remission (Gogokhia et al., 2025; Pinto et al., 2025; Raich et al., 2025; Zhang et al., 2024). This observation highlights the importance of the recipient’s microbiome ecological context, including niche availability, competitive pressure, and the capacity for restoration of key metabolic functions, in line with ecological models derived from analyses of mixed populations (Ianiro et al., 2022; Podlesny et al., 2022; Schmidt et al., 2022).

In this context, the concept of so-called keystone taxa has also been proposed—taxa exerting a disproportionately large influence on the stability and functioning of the microbial ecosystem. Originating from microbiome ecology and based on analyses of populations not restricted to IBD, this concept provides a useful interpretative framework for examining microbiome changes following FMT; at the same time, the available evidence in IBD is predominantly correlational and does not allow for the unequivocal attribution of causal roles to specific taxa. Consequently, the role of keystone taxa in modulating the efficacy of FMT remains a hypothesis requiring further validation in IBD-specific studies (Shin et al., 2024; Wilson, Vatanen, Cutfield, & O’Sullivan, 2019).

The aim of this study is to provide a narrative–systematic review of the literature published between 2015 and 2025 on the efficacy of FMT in IBD, with particular emphasis on donor microbiota engraftment processes, the potential role of keystone taxa, the donor effect phenomenon, and differences in response between UC and CD. This review integrates clinical, metagenomic, and ecological data into a coherent interpretative framework, enabling a better understanding of the mechanisms underlying the variable response to FMT in IBD.

## Methods

The study was conducted as a narrative–systematic review of the literature. Literature searches were performed in the PubMed/MEDLINE, Scopus, and Web of Science databases and supplementary searches were conducted using publisher search platforms (Elsevier, Springer, Frontiers, MDPI, and Wiley). A broad search strategy was applied, including keywords related to FMT, IBD, and gut microbiome analysis.

Publications were included if they addressed FMT in populations of patients with IBD and contained clinical data as well as microbiological analyses (16S rRNA sequencing, shotgun metagenomics, and strain-level analyses). Inclusion criteria comprised a publication period of 2015–2025 and adequate methodological quality, including randomized clinical trials, meta-analyses, as well as cohort and observational studies. The 2015–2025 time frame applied exclusively to analyses of the clinical efficacy of FMT and clinical outcome data in IBD.

Review, methodological, and mechanistic studies, as well as studies involving mixed populations not limited exclusively to patients with IBD, were used solely to establish the theoretical background and to aid in the interpretation of clinical findings, without being treated as evidence of FMT efficacy in UC or CD. In addition, two key studies published before 2015 (Morgan et al., 2012; Gevers et al., 2014) were used exclusively in the Introduction and in sections describing baseline gut microbiota characteristics in IBD and ecological concepts (including keystone taxa), solely to provide microbiological and ecological background.

A single case report (Lauridse et al., 2024) was also included in the analysis and was used exclusively to illustrate potential clinical effects of FMT in CD, without drawing any population-level conclusions.

In total, 34 publications were included in the final review as the most relevant to the objectives of this study.

## Results

### 1. Characteristics of the gut microbiota in patients with IBD before FMT

Analysis of the included studies demonstrated that the gut microbiota of patients with IBD prior to FMT is characterized by a markedly reduced alpha diversity, decreased abundance of short-chain fatty acid (SCFA)–producing bacteria, and a relative predominance of bacteria with potential pro-inflammatory activity, particularly those belonging to the phylum *Proteobacteria* (Aldars-García et al., 2021; Franzosa et al., 2019; Gevers et al., 2014; Halfvarson et al., 2017; Imhann et al., 2018; Lloyd-Price et al., 2019; Morgan et al., 2012; Ni et al., 2017; Pascal et al., 2017). The most frequently reported findings included a reduced representation of members of the families *Ruminococcaceae* and *Lachnospiraceae*, as well as *Faecalibacterium prausnitzii* (Gevers et al., 2014; Lloyd-Price et al., 2019; Pascal et al., 2017).

It was also demonstrated that baseline gut microbiota profiles differ between patients with CD and UC; despite these observations, a shared feature of both conditions is the presence of pronounced dysbiosis and disturbances in the metabolic potential of the gut microbiome (Franzosa et al., 2019; Imhann et al., 2018; Lloyd-Price et al., 2019).

Studies comparing responders and non-responders demonstrated that patients who achieved a clinical response after FMT—particularly in UC cohorts and in analyses including IBD populations—were characterized by higher baseline microbial diversity and a greater presence of selected commensal taxa compared with individuals who did not respond to treatment (Bénard et al., 2025; Zhang et al., 2024). Case-based data merely complement these observations and do not provide a basis for population-level conclusions (Lauridse et al., 2024). Very profound baseline dysbiosis was associated with poorer therapeutic outcomes, as supported by clinical studies in UC and analyses including IBD populations (Bénard et al., 2025; Zhang et al., 2024).

### 2. Clinical efficacy of FMT in IBD

Analysis of available studies indicates that the clinical efficacy of FMT is best documented in UC, as supported by meta-analyses and reviews including IBD populations (Caldeira et al., 2020; Imdad et al., 2018). A meta-analysis by Caldeira et al. demonstrated that FMT may lead to the achievement of clinical remission in a significant proportion of patients; however, the majority of interventional studies included in the analysis involved patients with UC (Caldeira et al., 2020). The Cochrane review reported an increased rate of clinical remission induction in active UC compared with placebo (risk ratio 1.79; 95% confidence interval 1.13–2.84) (Imdad et al., 2018), and subsequent systematic reviews likewise indicate a beneficial clinical effect of FMT in UC, with reservations related to protocol heterogeneity and small study sample sizes (Liu et al., 2023).

One of the key randomized clinical trials (Paramsothy et al., 2017) demonstrated that an intensive treatment regimen involving repeated administrations of FMT from multiple donors increased the rate of steroid-free clinical and endoscopic remission in active UC compared with placebo (27% vs 8%; risk ratio ~3.6;  $p = 0.021$ ). These findings are consistent with evidence from systematic reviews and meta-analyses, including that by Feng et al., which reported clinical improvement and a favorable safety profile of FMT in patients with active UC (Feng et al., 2023).

In CD, the efficacy of FMT remains more difficult to assess. Meta-analyses including IBD populations indicate that the available data for CD are limited and less conclusive than those for UC (Caldeira et al., 2020; Imdad et al., 2018). Nevertheless, observational studies and engraftment analyses suggest that a subset of patients with CD are likely to experience clinical improvement associated with a shift of the recipient's microbiome toward a donor-like profile (Kong et al., 2020; Lauridse et al., 2024).

In UC, maintenance of remission following FMT has been associated with stabilization of the recipient's microbiome and sustained taxonomic and functional changes (Pinto et al., 2025). In contrast, data on the durability of therapeutic effects in CD are scarce and are based primarily on small observational cohorts (Kong et al., 2020; Lauridse et al., 2024).

### 3. Microbiome changes after FMT

Interventional and observational studies—predominantly conducted in patients with UC—have shown that, in a subset of patients, FMT leads to an increase in alpha diversity and a shift of the recipient's microbiological profile toward that of the donor (Feng et al., 2023; Pinto et al., 2025; Raich et al., 2025). In CD, the available clinical data are more limited; however, observations from small cohort studies and clinical analyses indicate that a subset of patients may also exhibit microbiome shifts that can co-occur with clinical improvement (Kong et al., 2020), while isolated case reports serve only as supplementary evidence (Lauridse et al., 2024).

Engraftment analyses conducted in broader FMT populations—although not focused exclusively on IBD—suggest that similar donor strain colonization processes are likely to also occur in patients with IBD, supporting the biological plausibility of the observed microbiome changes (Podlesny et al., 2022).

Microbiological changes include partial normalization of the dysbiotic profile. Longitudinal data from studies of FMT in IBD indicate that maintenance of remission is associated with a sustained shift of the recipient's microbiota toward a donor-like profile (Pinto et al., 2025; Zhang et al., 2024).

At the same time, taxonomic changes following FMT have been shown to be accompanied by functional alterations, including restoration of bacterial metabolic functions and an increased potential for short-chain fatty acid production in studies conducted in patients with IBD (Raich et al., 2025). Mechanistic studies analysing strain dynamics in populations undergoing FMT for various indications—although not limited to IBD—suggest that processes of stable donor strain colonization may facilitate the persistence of functional changes in the gut microbiome (Ianiro et al., 2022; Schmidt et al., 2022).

Accumulated clinical data indicate that FMT leads to significant restructuring of the gut microbiome in a subset of patients with IBD (Pinto et al., 2025; Zhang et al., 2024). Mechanistic engraftment analyses performed in populations undergoing FMT for different indications—though not limited to UC or CD—demonstrate that the durability of microbiological changes may be supported by stable donor strain engraftment (Ianiro et al., 2022; Schmidt et al., 2022). These findings are consistent with observations of clinical efficacy in IBD but do not constitute direct evidence derived from UC- or CD-specific populations.

#### **4. Engraftment as a determinant of response**

An increasing body of evidence indicates that engraftment—defined as the stable colonization of the recipient's gut by donor strains—is a key determinant of FMT efficacy. Mechanistic studies based on strain-resolved metagenomics, conducted in mixed populations not restricted to IBD, have shown that high levels of engraftment involve entire functional bacterial consortia and may promote favorable metabolic changes, including an increased potential for short-chain fatty acid production (Ianiro et al., 2022; Podlesny et al., 2022; Schmidt et al., 2022). Although these studies were not performed specifically in IBD populations, they provide important mechanistic context for the interpretation of clinical data.

Clinical data in patients with IBD indicate that individuals who respond to FMT exhibit more stable occupation of intestinal niches by donor strains compared with non-responders (Zhang et al., 2024). Additionally, studies by Gogokhia et al. demonstrated that, in UC, both donor microbiota composition and dietary fiber supplementation are likely to facilitate more effective donor strain engraftment following FMT, highlighting the importance of dietary factors and donor microbiota quality in shaping post-transplant microbiome dynamics and, potentially, clinical response (Gogokhia et al., 2025).

In CD, the role of engraftment has been suggested by a study by Kong et al., in which stable colonization of the gut by donor strains was associated with maintenance of remission, whereas lack of engraftment correlated with disease relapse (Kong et al., 2020). Observations from small case series provide additional, albeit limited, evidence for similar associations (Lauridse et al., 2024).

Mechanistic analyses conducted in mixed populations provide important ecological context. Podlesny et al. showed that the durability of engraftment is influenced by so-called ecological fit, defined as the compatibility between the ecological and metabolic properties of the donor and recipient microbiota. This concept encompasses the availability of vacant ecological niches, the competitive capacity of donor strains, host-related perturbations of the gut ecosystem, and metabolic compatibility enabling stable coexistence within the gut ecosystem (Podlesny et al., 2022).

Overall, clinical data from patients with IBD, together with findings from mechanistic analyses, indicate that sustained engraftment of donor strains constitutes one of the key elements associated with the efficacy of FMT, facilitating long-term restructuring of the recipient's microbiota in both its composition and functional capacity (Ianiro et al., 2022; Kong et al., 2020; Podlesny et al., 2022; Schmidt et al., 2022; Zhang et al., 2024).

#### **5. Keystone species**

The concept of keystone taxa refers to microorganisms that perform critical ecological functions within microbiome interaction networks, exerting a disproportionately large influence—beneficial or detrimental—on ecosystem stability relative to their abundance. Identification of keystone taxa is typically based on network analyses, assessment of node centrality and “hubness,” evaluation of functional contributions to metabolic fluxes, and experimental reconstruction of stable bacterial consortia (Shin et al., 2024). In the context of IBD, the most frequently proposed candidates include taxa involved in maintaining key metabolic functions, such

as the production of short-chain fatty acids, as well as taxa modulating host immune processes (Franzosa et al., 2019; Lloyd-Price et al., 2019; Morgan et al., 2012; Ni et al., 2017; Pascal et al., 2017). Loss of these taxa represents a common feature of dysbiosis in IBD and is associated with destabilization of metabolic interactions and impaired regulation of inflammatory responses (Franzosa et al., 2019; Lloyd-Price et al., 2019; Ni et al., 2017).

Mechanistic analyses using strain-level metagenomics—conducted in mixed populations not limited to IBD—indicate that engraftment of keystone taxa following FMT may facilitate the reconstruction of functional modules within the microbiome and promote ecological stability (Ianiro et al., 2022; Podlesny et al., 2022; Schmidt et al., 2022; Shin et al., 2024). Strain-level studies further emphasize that durable colonization by donor strains is not random: stable engraftment more frequently involves taxa acting as metabolic hubs, whose presence enables the re-establishment of trophic interactions and metabolite fluxes within the gut ecosystem (Ianiro et al., 2022; Schmidt et al., 2022; Shin et al., 2024). This phenomenon is partially supported by clinical studies of FMT in IBD, in which treatment responders exhibit more stable functional integration of donor-derived taxa, associated with long-term alterations in microbiome structure (Zhang et al., 2024). In UC, it has additionally been shown that donor microbiota composition and dietary interventions (e.g., fiber supplementation) are likely to support the engraftment of taxa with high functional relevance, correlating with more stable microbiome reconstitution (Gogokhia et al., 2025).

Phenotypic differences between UC and CD suggest distinct sets of taxa that may fulfil keystone roles. In UC, where disruption of the butyrate-producing axis predominates, short-chain fatty acid (SCFA) producers are frequently proposed as key functional candidates, whose restoration is associated with the reconstruction of functional metabolic networks (Gogokhia et al., 2025; Zhang et al., 2024). The most frequently proposed keystone taxa in UC include butyrate producers such as *Faecalibacterium prausnitzii*, *Roseburia* spp., *Eubacterium rectale*, and selected species of the genus *Blautia*, which are involved in maintaining the butyrate axis and modulating host immune responses (Franzosa et al., 2019; Gogokhia et al., 2025; Lloyd-Price et al., 2019; Morgan et al., 2012; Ni et al., 2017; Pascal et al., 2017; Zhang et al., 2024). In CD—characterized by greater ecosystem instability—attention has been directed toward taxa with potential network-level significance, including certain *Bacteroides* species and bacteria associated with enhanced Th17-driven inflammatory responses, such as *Ruminococcus gnavus*. These taxa are more frequently observed in CD-associated dysbiosis and have been associated with ecosystem instability and reduced durability of donor strain engraftment (Franzosa et al., 2019; Gevers et al., 2014; Halfvarson et al., 2017; Kong et al., 2020; Lauridsen et al., 2024; Lloyd-Price et al., 2019; Ni et al., 2017). Their presence is not associated with maintenance of remission; on the contrary, increased abundance of *Ruminococcus gnavus* has been linked in multiple studies to active inflammation and an unfavorable microbial profile in CD (Franzosa et al., 2019; Gevers et al., 2014; Halfvarson et al., 2017; Lloyd-Price et al., 2019). Data regarding donor strain engraftment in CD remain limited and observational, without a clear association with clinical improvement (Kong et al., 2020; Lauridsen et al., 2024). Ecological models not directly related to IBD have further described that the stability of donor strain colonization may depend on ecological fit—a mechanism potentially relevant for interpreting the variability of engraftment observed in CD (Podlesny et al., 2022).

Overall, clinical data from IBD populations together with mechanistic ecological analyses suggest that keystone taxa are likely to contribute to the restructuring of the gut ecosystem following FMT. Sustained engraftment of such taxa—supported by ecological fit and the presence of functional metabolic modules—has been associated with durable microbiome reorganization and may represent one of several processes linked to the clinical efficacy of FMT in IBD (Gogokhia et al., 2025; Ianiro et al., 2022; Kong et al., 2020; Podlesny et al., 2022; Schmidt et al., 2022; Shin et al., 2024; Wilson et al., 2019; Zhang et al., 2024).

To organize the available evidence and highlight differences between the UC and CD phenotypes, Table 1 summarizes taxa proposed in the literature as candidates for keystone taxa, together with the direction of their impact on the gut ecosystem and the status of the available evidence.

**Table 1.** Keystone taxa and candidate keystone taxa in the context of FMT in IBD.

Taxon	IBD phenotype	Direction of ecosystem impact (keystone status/nature of effect)	Biological/functional rationale	Evidence status	Key references
<i>Faecalibacterium prausnitzii</i> (species)	UC	Candidate keystone*; potentially stabilizing	Butyrate producer; anti-inflammatory properties; frequently depleted in UC and associated with increased butyrogenic capacity and functional microbiome shifts following FMT	Clinical correlations (UC); no causal evidence	Bénard et al., 2025; Pinto et al., 2025; Zhang et al., 2024;
<i>Roseburia</i> spp. (genus)	UC	Candidate keystone*; potentially stabilizing	SCFA (butyrate) production; involvement in cross-feeding interactions and association with more stable metabolic network configurations	Clinical correlations (UC)	Bénard et al., 2025
<i>Eubacterium rectale</i> (species)	UC	Candidate keystone*; potentially stabilizing	SCFA (butyrate) producer; member of functionally relevant SCFA-producing taxa within the gut microbiome	Observational data; clinical correlations	Pinto et al., 2025
<i>Blautia</i> spp. (genus)	UC	Candidate keystone*; limited evidence	Putative network-associated taxon; involvement in fermentation processes	Limited observational data	Bénard et al., 2025; Franzosa et al., 2019
<i>Bacteroides</i> spp. (selected species)	CD	Context-dependent candidate; species- and niche-specific effects	Heterogeneous genus; context-dependent network associations; no consistent beneficial signature	Small cohorts; inconclusive clinical data	Halfvarson et al., 2017; Lloyd-Price et al., 2019
<i>Parabacteroides</i> spp. (genus)	CD	Hypothetical candidate; unclear role	Observed in selected engraftment analyses; no clearly stabilizing function identified	Observational data; no validation	Kong et al., 2020
<i>Ruminococcus gnavus</i> (species)	CD	Candidate keystone*; potentially destabilizing	Pathobiont; correlations with inflammation; potential disproportionate impact on interaction networks and maintenance of dysbiosis	Clinical correlations; no causal evidence	Kong et al., 2020; Lloyd-Price et al., 2019; Pascal et al., 2017

\*The term “candidate keystone” refers to taxa whose disproportionate impact on microbiome structure and function is suggested based on clinical correlations and ecological observations; direct causal evidence confirming their keystone status in human interventional studies is currently lacking

## 6. Donor effect

The efficacy of FMT shows substantial interindividual variability, which has been described as the so-called donor effect—a term referring to differences in therapeutic outcomes associated with variability in the composition and functional potential of the donor microbiota (Wilson et al., 2019). This phenomenon has been most clearly documented in clinical studies of FMT in UC, where material derived from different donors varied in therapeutic potential and correlated with the rate of clinical response achieved (Paramsothy et al., 2017; Pinto et al., 2025).

Clinical reviews and methodological analyses further emphasize that donor microbiota characteristics—including alpha diversity, functional profile, and the capacity for stable colonization—constitute important determinants of heterogeneous therapeutic outcomes (Steube et al., 2023). In a randomized controlled trial, Paramsothy et al. additionally demonstrated that an intensive multidonor treatment regimen increased remission rates in patients with active UC, supporting the hypothesis that donor-related features influence therapeutic efficacy, while simultaneously highlighting the role of administration protocols and the use of

donor mixtures (Paramsothy et al., 2017). Longitudinal analyses in UC patients further confirm that donor taxonomic and functional profiles, as well as trajectories of stable donor strain engraftment following FMT, correlate with the achievement of clinical response (Pinto et al., 2025; Raich et al., 2025).

In CD, available data are considerably more limited. Metagenomic analyses of small case series suggest an association between the degree of engraftment and maintenance of remission (e.g., Kong et al., small cohort of patients undergoing FMT), while isolated case reports have documented clinical remission and shifts in the recipient microbiome following FMT. Given the small sample sizes and observational nature of these reports, they should be interpreted as hypothesis-generating signals rather than definitive evidence of a population-level effect (Kong et al., 2020; Lauridse et al., 2024). In CD, the donor effect appears to be more difficult to predict; substantial variability in engraftment is observed, which may reflect greater heterogeneity of the recipient microbiota, varying degrees of dysbiosis, and distinct patterns of donor strain colonization (Kong et al., 2020). However, these observations require confirmation in larger, well-controlled cohorts (Kong et al., 2020; Lauridse et al., 2024).

Mechanistic studies—often conducted in mixed populations and of a model-based nature—provide conceptual frameworks for explaining the variability of the donor effect. Metagenomic analyses and ecological studies indicate that successful engraftment depends, among other factors, on *ecological fit*—defined as ecological and metabolic compatibility between donor and recipient microbiota—including the availability of ecological niches, the intensity of competitive pressure (including priority effects), and trophic and functional compatibility. Although these concepts are supported by substantial theoretical and observational evidence, most available data remain model-based or observational and have not yet been conclusively validated in cohorts restricted exclusively to UC or CD (Ianiro et al., 2022; Podlesny et al., 2022; Schmidt et al., 2022).

The literature also introduces the concept of so-called “super-donors”—donors with particular microbiological profiles (e.g., high microbial diversity, the presence of potential keystone taxa, and favorable functional characteristics), whose stool material has been associated with improved clinical outcomes; at the same time, this remains largely an observational and conceptual hypothesis that requires further investigation (Wilson et al., 2019).

Taken together, evidence from clinical reviews, meta-analyses, and mechanistic studies suggests that the donor effect arises from complex interactions between donor-related features and recipient-specific characteristics, rather than representing a fixed property of the donor alone (Steube et al., 2023; Wilson et al., 2019). Cohort studies and longitudinal metagenomic analyses conducted predominantly in UC indicate that variability in donor microbiota composition, together with differences in baseline recipient microbiome structure, are associated with post-transplant engraftment dynamics and clinical outcomes (Pinto et al., 2025; Zhang et al., 2024). By contrast, evidence in CD remains limited; available data are restricted to small cohorts and isolated case reports, which describe heterogeneous engraftment patterns and occasional clinical improvement following FMT. Given the observational nature and limited sample sizes of these studies, such findings should be interpreted as hypothesis-generating rather than as evidence of a consistent population-level donor effect in CD (Kong et al., 2020; Lauridse et al., 2024).

## 7. UC vs CD differences

Clinical response to FMT differs between UC and CD, reflecting differences in the nature of dysbiosis and in the stability of the gut ecosystem across these two IBD phenotypes. Studies describing baseline gut microbiota prior to treatment indicate that UC and CD are characterized by distinct taxonomic profiles and by different depths of functional disruption, which may influence the capacity for donor strain colonization following FMT (Gevers et al., 2014; Halfvarson et al., 2017; Lloyd-Price et al., 2019).

### Ulcerative colitis

In UC, a more predictable and consistent pattern of response to FMT has been documented. The randomized trial by Paramsothy et al. demonstrated higher rates of clinical remission following an intensive multidonor regimen (Paramsothy et al., 2017), and these findings are supported by studies assessing microbiome dynamics after FMT (Feng et al., 2023; Pinto et al., 2025). Longitudinal analyses indicate that patients who respond to therapy more frequently exhibit stable engraftment of donor strains and a more consistent reconstruction of microbiome functions, encompassing both taxonomic and functional components. These associations are correlational in nature and require confirmation in larger, well-controlled clinical cohorts (Pinto et al., 2025; Raich et al., 2025). In the context of FMT in UC, clinical response has often been accompanied by an increase or maintenance of butyrate-producing taxa—particularly *Faecalibacterium prausnitzii* and taxa assigned to the genus *Roseburia*—which correlates with functional reconstruction of the butyrogenic axis following successful FMT; however, these observations remain correlational and require further validation (Bénard et al., 2025; Pinto et al., 2025).

### Crohn's disease

In CD, the response to FMT is markedly more heterogeneous. Clinical data are limited to small cohorts in which the degree of engraftment has been shown to correlate with maintenance of remission in a subset of patients; nevertheless, response rates remain lower and less stable than those observed in UC (Kong et al., 2020). Isolated case reports document the possibility of achieving remission and shifts in microbiome profiles following FMT, but these observations are illustrative in nature and cannot serve as a basis for population-level conclusions (Lauridse et al., 2024). The limited predictability of FMT outcomes in CD may reflect greater heterogeneity of the gut microbiota, distinct patterns of dysbiosis, and more frequent destabilization of ecological niches. In contrast to UC, no clear, universal, and reproducible taxonomic signature fulfilling the role of potential “keystone species” has emerged in CD; although some studies propose candidate signature taxa, reproducibility across cohorts remains limited (Gevers et al., 2014; Halfvarson et al., 2017; Lloyd-Price et al., 2019). Nevertheless, many analyses have highlighted a higher prevalence of pro-inflammatory taxa, such as *Ruminococcus gnavus*, along with a reduced abundance of SCFA-producing bacteria, which has been associated with an unfavorable microbial environment in CD and may hinder stable donor strain colonization (Kong et al., 2020; Pascal et al., 2017).

### Summary

Available clinical and ecological data indicate that differences in response to FMT between UC and CD arise primarily from distinct properties of the gut ecosystem, including niche stability, the depth of dysbiosis, and the capacity for integration of donor-derived strains. In UC, more coherent and predictable patterns of colonization are observed, along with higher rates of clinical response, whereas in CD the efficacy of FMT is more variable and more strongly dependent on individual donor–recipient interactions and on the degree of disruption of the gut ecosystem (Feng et al., 2023; Kong et al., 2020; Pinto et al., 2025; Raich et al., 2025).

### Discussion

This review indicates that the efficacy of FMT in IBD cannot be interpreted solely in terms of a simple “restoration of microbial diversity.” Accumulated clinical and metagenomic data suggest that FMT represents a complex ecological intervention, the therapeutic effect of which is linked to the capacity of donor microbiota to achieve durable integration within the recipient gut ecosystem, reconstruction of key metabolic functions, and modulation of microbial interaction networks. From this perspective, FMT is not a one-time transfer of microorganisms, but rather a process of gut ecosystem reorganization, the course and durability of which are determined by interactions between donor and recipient microbiota. Within this conceptual framework, processes of donor strain engraftment and the role of taxa exerting potentially disproportionate effects on ecosystem stability—referred to as keystone taxa—assume central importance.

#### 1. Engraftment as a necessary but insufficient condition for FMT efficacy

Analysis of the available evidence indicates that stable engraftment of donor microbiota constitutes a key component of response to FMT, particularly in UC, where its presence has repeatedly correlated with clinical remission and functional restoration of the gut microbiome (Pinto et al., 2025; Zhang et al., 2024). At the same time, these data emphasize that colonization per se is not synonymous with clinical improvement. Engraftment should therefore be viewed not as a binary indicator of success, but as a dynamic process, the therapeutic relevance of which depends on the quality of the engrafting strains, their metabolic functions, and their capacity to integrate into pre-existing interaction networks.

This framework helps explain why comparable levels of microbial diversity following FMT are likely to be associated with divergent clinical outcomes. Analysis of available studies indicates. Functional reconstruction—particularly restoration of the butyrogenic axis and related metabolic pathways—may play a more decisive role in maintaining remission than taxonomic shifts alone. From an ecological perspective, this implies that FMT efficacy is closely linked to the restoration of specific system-level functions, rather than to normalization of microbiota composition per se.

#### 2. Keystone taxa as potential regulators of gut ecosystem stability

Within this conceptual framework, the concept of keystone taxa provides a useful interpretative lens for understanding why relatively small changes in microbiome structure can lead to disproportionately large functional effects. Keystone taxa do not need to be dominant components of the microbiota; rather, their importance arises from their central position within metabolic and trophic interaction networks and their capacity to modulate ecosystem stability (Shin et al., 2024). Importantly, the influence of such taxa can be

either stabilizing or destabilizing from the host perspective. In human microbiome research, the identification of keystone taxa remains methodologically heterogeneous and is typically based on a combination of network centrality analyses, inferred functional relevance, strain persistence, and clinical correlations, rather than on direct experimental validation.

In UC, clinical data indicate that response to FMT is often accompanied by an increase or maintenance of short-chain fatty acid-producing taxa, such as *Faecalibacterium prausnitzii* and members of the genus *Roseburia*. These changes correlate with restoration of microbiome metabolic functions and features suggestive of greater gut ecosystem stability (Bénard et al., 2025; Pinto et al., 2025). Accordingly, these taxa can be regarded as candidates for stabilizing keystone taxa in this disease phenotype. Nevertheless, the available evidence is predominantly correlational and does not allow for definitive attribution of a causal role.

A different situation is observed in CD, where greater instability of the gut ecosystem and the presence of pathobionts, such as *Ruminococcus gnavus*, are associated with persistence of inflammation and a reduced capacity for integration of beneficial donor-derived strains (Kong et al., 2020; Pascal et al., 2017). In this phenotype, putative “negative” keystone taxa may function as destabilizing factors, whose persistence hinders the achievement of durable therapeutic effects despite transient engraftment.

### 3. Donor effect and ecological fit as a donor–recipient interaction

Variability in clinical response to FMT, referred to as the donor effect, can be interpreted in light of ecological concepts such as ecological fit. Metagenomic analyses and ecological models suggest that therapeutic success does not depend solely on the intrinsic quality of the donor microbiota, but rather on ecological and metabolic compatibility between donor microbiota and the recipient gut environment, encompassing the availability of vacant niches, competitive pressure, and functional compatibility (Ianiro et al., 2022; Podlesny et al., 2022; Schmidt et al., 2022). Notably, in the context of IBD, ecological fit currently represents a hypothesis-generating framework rather than a clinically validated predictive tool.

Within IBD populations, the significance of the donor effect is best documented in UC, where clinical studies have demonstrated substantial differences in FMT efficacy depending on the donor material used. These data indicate that even microbiota with high diversity do not invariably lead to durable clinical responses if stable functional integration within the recipient ecosystem is not achieved.

In CD, available observations are more limited and point to greater variability in engraftment and reduced predictability of clinical outcomes, further underscoring the importance of donor–recipient interactions and gut ecological conditions.

Understood in this way, the donor effect is not a fixed property of the donor, but rather an emergent outcome of interactions between donor and recipient microbiota within a given ecological context. This perspective also allows reinterpretation of the concept of so-called “super-donors”—not as universally effective sources of microbiota, but as donors whose microbiomes display high adaptive capacity in specific ecological contexts (Wilson et al., 2019). Consequently, the efficacy of a given donor may depend on disease phenotype, the degree of dysbiosis, and individual characteristics of the recipient microbiome, thereby explaining the limited reproducibility of results across clinical studies.

### 4. Differences between UC and CD in the context of microbiome ecology

One of the most important conclusions emerging from this review is the clear differentiation of mechanisms underlying response to FMT between UC and CD. In UC, a more predictable pattern of clinical response is observed, suggesting that the gut ecosystem in this phenotype retains a greater capacity for reorganization and stabilization following microbiological intervention (Feng et al., 2023; Pinto et al., 2025). In CD, by contrast, the depth of dysbiosis, fragmentation of ecological niches, and microbiome heterogeneity contribute to substantially greater variability in response and to limited durability of clinical effects (Halfvarson et al., 2017; Kong et al., 2020; Pascal et al., 2017).

These observations indicate that FMT should not be regarded as a uniform therapeutic approach for all forms of IBD in the current state of knowledge. Consideration of disease phenotype and the ecological properties of the recipient microbiome appears to be critical for interpreting existing evidence and for the design of future therapeutic strategies. At present, available data do not allow for reliable stratification of CD subphenotypes with respect to FMT responsiveness.

### 5. Methodological implications and future research directions

From both clinical and research perspectives, this analysis underscores the need to move beyond simple measures of FMT efficacy toward more complex indicators encompassing engraftment stability, functional reconstruction, and the dynamics of microbiome interaction networks. In the current state of evidence, FMT is currently best viewed as an adjunctive rather than a stand-alone therapeutic strategy in IBD. The development of standardized engraftment metrics and prognostic tools enabling assessment of ecological fit prior to intervention may, in the future, represent an important step toward the personalization of FMT.

At the same time, it is important to recognize that a substantial proportion of studies analysed in this review are based on small patient cohorts and, in the case of CD, also on observational series and case reports, which limits the generalizability of the conclusions.

Interventional and experimental studies are therefore required to validate the roles of proposed keystone taxa and to distinguish correlational associations from causal effects. Until such evidence becomes available, the concept of keystone taxa should be regarded as a useful yet still hypothetical interpretative framework for understanding the efficacy of FMT in IBD.

### Conclusions

Accumulated evidence indicates that the efficacy of FMT in IBD cannot be interpreted solely as an effect of restoring microbial diversity, but rather as the outcome of a complex ecological intervention. A central component of this intervention is stable, functional engraftment of donor microbiota—a dynamic process of integration within the recipient gut ecosystem.

Analysis of available studies suggests that engraftment represents a necessary, but not sufficient, condition for achieving clinical response. The effectiveness of FMT depends on functional reconstruction of the gut ecosystem, encompassing both restoration of key metabolic pathways and reorganization of microbial interaction networks.

The concept of keystone taxa provides a useful interpretative framework for understanding the disproportionate influence of selected taxa on microbiome function following FMT in IBD. However, the current body of evidence is predominantly correlational, supporting the view that keystone taxa should be regarded as candidates requiring further validation in interventional studies.

Variability in the efficacy of FMT among patients, referred to as the donor effect, constitutes an emergent outcome of interactions between donor and recipient microbiota rather than a fixed property of the transplanted material. From this perspective, *ecological fit*—the ecological and metabolic compatibility between donor microbiota and the recipient gut environment—emerges as a key determinant of engraftment durability.

An important conclusion of this review is the clear differentiation of mechanisms underlying response to FMT between UC and CD. In UC, clinical response and microbiota colonization following FMT are more predictable, whereas in CD therapeutic efficacy remains more variable and more strongly dependent on individual properties of the gut ecosystem.

Taken together, the presented data indicate the need for a paradigm shift in the evaluation of FMT toward an approach that incorporates engraftment stability, functional reconstruction of the microbiome, and the ecological context of the recipient. The development of standardized engraftment metrics and prognostic tools may, in the future, enable a more rational and personalized application of FMT in the treatment of IBD.

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