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Gut Microbiome Alterations in Inflammatory Bowel Disease: A Narrative Review of Sequencing Studies

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ABSTRACT

Inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, is consistently accompanied by a shift in the composition of the intestinal microbial community, and sequencing has made that shift measurable. This narrative review asks what the sequencing literature does and does not establish. It draws on published work on amplicon and shotgun methods, on cross-sectional and longitudinal cohorts, on fungal and viral communities, and on microbial metabolites and immune signalling, and it reports no new data. The most repeated observations are lower diversity, fewer butyrate-producing Firmicutes and a relative gain of facultative anaerobes such as Enterobacteriaceae, with differences between Crohn's disease and ulcerative colitis and between ileal and colonic disease. Much of this signal is entangled with inflammation, diet, medication and bowel habit, and most studies are cross-sectional, so cause and consequence are hard to separate. Compositional data, small cohorts, contamination and uneven methods add further uncertainty. The review concludes that dysbiosis is a robust description but a weak explanation, and it lists the designs that would move the field from association towards mechanism and clinical use.

Keywords: Inflammatory bowel disease; Gut microbiome; Dysbiosis; 16S rRNA sequencing; Shotgun metagenomics; Short-chain fatty acids; Narrative review

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Article Class: Review Article

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic, relapsing conditions of the gut, of which Crohn's disease and ulcerative colitis are the two principal forms. Crohn's disease can involve any

segment of the digestive tract with inflammation that crosses the bowel wall (1), whereas ulcerative colitis is confined to the colon and rectum and affects the mucosa in a continuous pattern (2). Both have become more common in newly



industrialising regions while remaining frequent in the West (3), a pattern that points to environmental change as well as inherited risk.

The microbial community of the intestine has been a suspect for a long time. Many of the genetic risk loci for IBD lie in pathways that sense microbes or defend the mucosa (4), and the disease is rarely found where there are no bacteria to react to. When high-throughput sequencing arrived, it became possible to ask what the community in patients actually looks like, without growing anything in a dish. The answer, repeated in study after study, is that it looks different from the community in healthy people (5, 6).

What a difference means is a harder question. A community can change because it causes disease, because disease changes the gut, or because something else, such as a course of antibiotics, changes both. This review sets out what the sequencing literature reports about the gut microbiome in IBD, how the methods shape those reports, and how much explanatory weight the findings can carry. It is a narrative review of published work and reports no new data; where a reader might want a figure for the size of an effect, we point to the original papers instead of quoting numbers from memory. The aim is a fair account of what has been measured and what has merely been repeated.

2. Literature Review

2.1 A Healthy Reference and What Sequencing Added

Large metagenomic projects defined what a healthy gut community looks like in broad terms. A catalogue of microbial genes assembled from human faecal samples showed how many genes the community carries and how much is shared between people (7), and the Human

Microbiome Project mapped the structure and diversity of communities at several body sites in healthy adults (8). These resources are the yardstick against which patient samples are compared, and they carry the caveat that healthy volunteers are themselves a selected group.

Healthy variation is wide. Population studies that measured thousands of people found that diet, medication, stool consistency and many host traits all leave a mark on the community (9, 10). The practical consequence is that a case-control difference in IBD must be large enough, and consistent enough, to stand out against a background that is already noisy. Figure 1 sketches the working model that most of the literature adopts, in which host and environmental factors shape the community, the community influences the barrier and the immune system, and inflammation feeds back on the community.

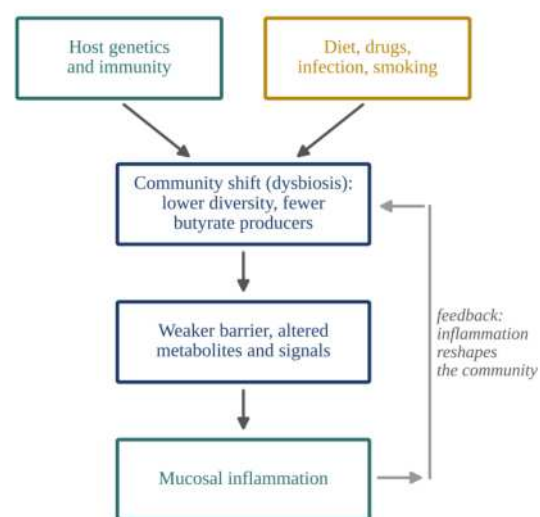


Figure 1. A working model linking host, environment and microbes, with a feedback loop (schematic, not data).

2.2 Bacterial Signatures in Crohn's Disease and Ulcerative Colitis

The earliest sequencing studies reported a loss of diversity, with fewer Firmicutes and Bacteroidetes and a relative gain of



Proteobacteria and Actinobacteria in IBD (5). Work using a metagenomic approach in Crohn's disease confirmed lower diversity in faecal samples, most clearly within the Firmicutes (6). One of the most cited findings concerns *Faecalibacterium prausnitzii*, a butyrate producer that was reduced in patients with ileal Crohn's disease and that showed anti-inflammatory activity in experimental systems (11). A similar loss of butyrate-producing species, including *Roseburia hominis*, has been described in ulcerative colitis (12). Table 1 collects the alterations that recur most often.

Table 1. Alterations most often reported in inflammatory bowel disease.

Feature	Usual direction	Caveat
Overall diversity	Lower (6, 13)	Partly tracks inflammation and stool form
Butyrate producers	Fewer (11, 12)	Also reduced by antibiotics and diet change
Enterobacteriaceae	Relatively more (14, 15)	Bloom with oxygen and inflammation
Fungi	Community shifted (16)	Few cohorts; methods vary
Viruses	Altered virome (17)	Reference databases are sparse
Stability over time	More fluctuation (18)	Needs repeated sampling

Note: Qualitative summary of direction only. Findings differ between cohorts, sites and disease phenotypes, and no magnitudes are given.

At the other end of the scale, facultative anaerobes tend to increase. Adherent-invasive *Escherichia coli* were found far more often on the ileal mucosa of people with Crohn's disease than in controls (14), and a study of untreated children with new-onset Crohn's disease reported expansion of Enterobacteriaceae

and other families alongside losses in several obligate anaerobes (13). Pooled signatures built from several cohorts converge on the same broad picture, a drop in butyrate producers with a rise in species that tolerate inflammation (15, 19).

Disease subtype matters. Studies of twins found that communities differ between ileal and colonic Crohn's disease, so that the label Crohn's disease hides at least two ecological situations (20). Ulcerative colitis, which is confined to the colon, tends to show a milder reduction in diversity than ileal disease. Pooling subtypes into one patient group, as many early studies did, can blur differences that matter. Such differences look small in a single sample, yet they add up across a cohort.

2.3 Fungi and Viruses

Bacteria are only part of the community. Reviews of the field stress that fungi and viruses may also contribute to disease and that they have been studied far less (21). In IBD cohorts, fungal profiling has described a shifted balance, with a relative fall in *Saccharomyces cerevisiae* and a rise in *Candida albicans* (16). Studies of the enteric virome found altered bacteriophage communities that differed between Crohn's disease and ulcerative colitis (17). Reference databases for fungi and viruses are small, so these pictures are sketches next to the bacterial draft.

2.4 From Taxa to Function: Metabolites, Barrier and Immunity

The reason to care about which species change is that they do things. Bacterial fermentation of fibre produces short-chain fatty acids, and butyrate in particular is a fuel for colonocytes and a signal that promotes regulatory T cells in the colon (22, 23). Loss of the producers would therefore be expected to weaken both energy supply and immune restraint. Other



microbes push in the opposite direction; in mice, segmented filamentous bacteria drive the development of Th17 cells (24), a reminder that the same community can tune the immune system towards tolerance or towards activation.

Bile acids tell a similar story. Patients with IBD have been reported to carry altered bile-acid profiles, with a shortfall of microbially produced secondary forms (25), and recent reviews list tryptophan metabolites and other products as further candidates for mediating the community's effects (26). In an inflamed gut the mucus layer that normally keeps bacteria at a distance from the epithelium is thinner or breached (27), which changes how much of any metabolite the host tissue sees.

Multi-omic studies now measure species, genes, transcripts and metabolites in the same samples. Their general finding is that functional and metabolic profiles are often more disturbed in disease than species lists alone would predict (15, 28). Early work on microbial gene content in IBD, and on the effect of treatment, already pointed in this direction (29).

3. Materials and Methods

3.1 Scope and Question

The review asks one question in two parts. First, what alterations in the gut community of people with IBD have been described using sequencing? Second, how strongly do the designs and methods of those studies support the idea that the alterations explain the disease, as opposed to accompanying it? To keep the question tractable, it was divided into the matters a study would have to settle: how samples were collected, what was sequenced, how data were analysed, how medication and diet were handled, and whether samples were taken once or repeatedly. None of these choices is exotic, but each one limits what the review can claim.

3.2 Literature Assembly

The review draws on peer-reviewed work in five areas: the healthy reference microbiome; cohort and case-control studies of IBD; fungal and viral profiling; mechanistic work on metabolites, barrier function and immunity; and the methodological literature on sequencing and analysis. Sources were chosen for relevance, influence in the field and clarity of method, and the choice reflects the authors' judgement. We did not run a formal systematic search, and we make no claim to one. This is a narrative synthesis.

We avoid quoting prevalence figures, effect sizes or counts from individual papers, because we could not check them against the primary reports for this article. Table 2 lists the sequencing approaches that appear in the literature and the limits we kept in mind when reading them.

Table 2. Sequencing approaches used in microbiome studies of the disease.

Approach	What it gives	Main limit
16S rRNA amplicons	Taxonomic profile at modest cost (30)	Genus-level resolution; no function
Shotgun metagenomics	Strains and gene content (31)	Cost; host DNA; depth
Metatranscriptomics	Which genes are active (15)	RNA is fragile; few cohorts
Metabolomics	Small molecules and bile acids (25, 28)	Diet and drugs confound
Quantitative profiling	Cell counts, not only ratios (32)	Extra assays; rarely done

Note: Strengths and limits are those described in the methodological literature, not attributed to any single study.

3.3 Appraisal Framework

To judge how far a finding can be trusted, we asked four questions of each body of



evidence. Was the design able to separate cause from consequence, for example by sampling the same people over time (18, 33)? Were medication, diet and stool characteristics recorded and handled (10, 34)? Were the data analysed in a way that respects their compositional nature (35)? And were contamination and reagent effects controlled (36)? These questions are not a scoring system; they are a way of deciding how much weight to put on a given claim. A clinician reading a cohort paper needs to know whether the finding would hold in the next patient.

4. Results

4.1 What the Cohorts Agree On

Across cohorts and methods, three observations recur. Diversity is lower in IBD than in controls, butyrate-producing Firmicutes are depleted, and facultative anaerobes, especially members of the Enterobacteriaceae, are enriched (6, 11, 13). The pattern is more marked in Crohn's disease than in ulcerative colitis and more marked in active disease than in remission (15, 19). Figure 2 summarises the direction of these changes without implying anything about their size.

	Crohn's disease	Ulcerative colitis
Overall diversity	Lower	Lower, milder
Butyrate producers	Fewer	Fewer
Enterobacteriaceae	More	More
Fungal community	Shifted	Shifted
Virome	Altered	Altered

Blue lower, orange higher, grey shifted: direction only; schematic, not data

Figure 2. Direction of change most often reported, by feature and disease (qualitative schematic, not data).

The agreement is real, but it is agreement about a pattern and not about a list of species. Different studies nominate different taxa within the same functional groups, and a species named in one cohort is often absent from the next. That is partly biology, since different species can fill the same ecological role, and partly the result of different methods and different populations (9). The safest reading is that the functional shift, from fibre fermenters to inflammation-tolerant organisms, is better supported than any particular species. This is why the same disease can look quite different from one cohort to the next.

4.2 Instability Over Time

Longitudinal sampling adds something that single samples cannot. In a Swedish cohort followed over time, people with IBD, particularly Crohn's disease, showed more fluctuation in community composition than healthy controls, and the pattern differed with disease location (18). A large multi-omic study that followed participants through periods of activity and quiet described stretches in which the community departed sharply from its usual state, accompanied by shifts in metabolites (15).

This has a direct consequence for design. A single cross-sectional sample captures one moment, and whether a patient looks dysbiotic on the day of sampling depends partly on where they are in their cycle of flare and remission. A gut sampled once is a photograph, and the disease is a film. Studies that compare one sample per person are measuring an average of unstable states, and their conclusions should be framed accordingly.

4.3 How Much of the Signal Is the Disease?

Cross-cutting factors complicate the picture (Table 3). Analyses that put IBD



cohorts alongside irritable bowel syndrome and healthy controls, and that recorded drug use, found that part of the apparent disease signal could be attributed to medication and other factors rather than to the diagnosis (34). In children, antibiotics and diet were associated with their own shifts in the community (37). Population studies had already shown that stool consistency and common drugs shift the community in people without IBD (9, 10).

Table 3. Common weaknesses in microbiome studies of the disease and how they distort findings.

Weakness	Consequence	Remedy
Cross-sectional design	Cause and effect indistinct (33)	Repeat sampling (18)
Relative abundance only	Apparent rises and falls (35)	Compositional methods; load
Medication and diet	Alter taxa directly (37, 38)	Record and adjust (34)
Contamination	Spurious taxa in low-biomass samples (36)	Negative controls
Small cohorts	Unstable lists of taxa (9)	Larger, multi-site studies

Note: Weaknesses are those discussed in the cited methodological and cohort literature; they are not attributed to any one study.

Measurement adds a further layer. Most sequencing studies report relative abundance, so that a rise in one group makes every other group appear to fall, and the compositional nature of such data can produce spurious correlations unless it is handled explicitly (35). When absolute microbial load was measured alongside composition, load emerged as a major driver of variation and a source of confounding in disease comparisons (32). Contamination from reagents can create apparent taxa in samples with little genuine microbial material (36), which matters most for mucosal biopsies and low-biomass sites. A signal that vanishes once medication is accounted for is not a

signal about the disease.

4.4 Evidence From Intervention

If dysbiosis drove disease, changing the community should change the disease. Faecal microbiota transplantation, the most direct test, has been examined in ulcerative colitis in randomised trials. Two trials reported higher remission rates with donor material than with placebo (39, 40), while another did not reach its primary endpoint (41). The trials differed in route, schedule and donor, and what is transferred is not yet well characterised.

These trials are encouraging, but they do not settle the question. A therapy can work through a pathway that is not the cause of the disease. Figure 3 arranges the types of study by how close they come to answering the causal question.

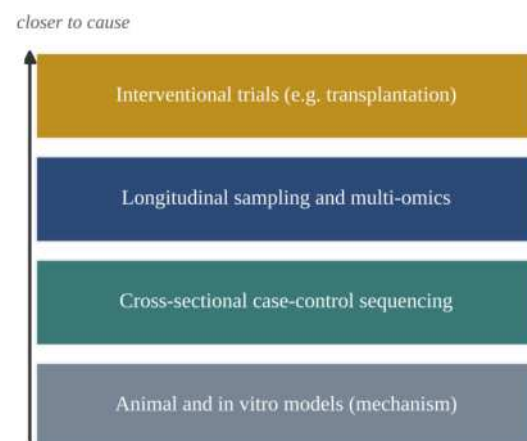


Figure 3. Layers of evidence from association towards intervention; heights are not counts (schematic).

Put plainly, the literature supports a cautious statement. The gut community of people with IBD differs from that of controls in a consistent functional direction, the difference is partly explained by inflammation, drugs and diet, and interventional evidence that altering the community alters the disease is promising but incomplete.



5. Discussion

5.1 Interpretation

The main finding of this review is a conditional one. Dysbiosis in IBD is a robust description, but it is a weak explanation. It tells us that something in the gut has changed, and it does not tell us which change comes first. The case for a causal role rests on the genetic link to microbial sensing (4), on mechanistic work with metabolites and immune cells (22, 23, 26), and on the transplantation trials. The case against treating it as settled rests on instability over time, on confounding by drugs and diet, and on the fact that inflammation reshapes the community (33, 42).

A second conditional concerns generality. Findings from a hospital cohort in one country, sampled during a particular phase of disease and analysed with one pipeline, may not transfer to another population or method. Differences in diet, environment and background community mean that a marker which works in one setting can fail in another (9, 43). Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

Three findings would change this reading. A well-controlled longitudinal study showing community change reliably preceding relapse, after accounting for drugs and diet, would strengthen the causal view. A trial demonstrating that a defined, characterised consortium induces remission would move the field from donor material to a product. And evidence that the functional signature is the same across populations and methods would justify its use as a diagnostic or monitoring tool; so far, the data are too uneven to say.

5.2 Limitations

This is a narrative review and shares the limits of that form. The selection of

sources reflects judgement, no formal search or quality scoring was done, and we do not quote numerical results from individual studies because they could not be checked against the primary papers for this article. A reader who needs an effect size should consult the original reports directly, or a formal systematic review. The review also leans heavily on work from a limited set of well-funded research groups, and populations outside Europe and North America are under-represented in the literature on which it draws (3). Fungal and viral communities, host genetics and paediatric onset all deserve fuller treatment than a review of this length allows. The point is not that these studies are poor, only that their conclusions travel less far than their abstracts suggest.

5.3 Directions for Future Work

Three needs stand out. First, longitudinal cohorts with dense sampling around flares, with diet and drug use recorded carefully and analysed in a compositionally aware way (18, 35), preferably with measurement of microbial load (32). Second, studies that combine species-level or strain-level sequencing with metabolites and host response, so that function can be linked to the organisms responsible (28, 31). Third, trials of defined interventions with pre-specified outcomes and enough participants to reveal what drives response, including donor effects (39, 40). Read this way, a null result in a small cohort is not evidence of absence. Reporting should also be standardised, since authors who state the extraction method, the negative controls and the handling of covariates make pooling possible. It is a habit worth keeping even when the result is the expected one.

6. Conclusion

The gut microbiome in IBD is altered in ways that sequencing has described



consistently: lower diversity, fewer butyrate-producing organisms and more facultative anaerobes, together with shifts in fungi, viruses and metabolites. What the literature has not yet established is whether these changes drive disease, follow from it, or both in turn. The weight of the evidence supports a feedback model in which host, environment and community interact, and inflammation reshapes the community that provoked it. Nothing here argues against studying the microbiome; it argues for asking sharper questions of it.

For the practitioner, the message is one of calibrated interest: the microbiome is a legitimate target of research and early intervention, though no sequencing profile is yet a reliable tool for individual patients. For the researcher, the opportunity lies in longitudinal, well-controlled, mechanistically informed studies that move the field from description towards explanation. These cautions apply with equal force to many other conditions that have been studied in the same way.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

C.M. conceived the review and wrote the sections on sequencing methods and interpretation. C.H. wrote the sections on fungal and viral communities and on metabolites. H.H. wrote the sections on clinical features, intervention studies and trial design. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No human participants or animals were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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