DOI: 10.66069/ojspub.27450740

Gut Microbiota Dysbiosis in Colorectal Polyp Formation and Progression: Mechanisms, Biomarkers, and Therapeutic Potentials

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Abstract: ***Colorectal polyps, particularly adenomatous polyps, are well-established precursor lesions for colorectal cancer (CRC). Although endoscopic polypectomy effectively removes visible lesions, the postoperative recurrence rate remains persistently high (ranging from 30% to 40%), highlighting an urgent need to address the underlying systemic microenvironment that fosters polyp emergence. In recent years, accumulating evidence has positioned gut microbiota dysbiosis as a pivotal, modifiable driver in the initiation and malignant transformation of colorectal polyps. This review systematically synthesizes current mechanistic insights into how microbial perturbations contribute to colorectal polypogenesis. We delineate three interconnected pathogenic cascades: (1) direct genotoxicity, primarily mediated by pathogens such as pks⁺ Escherichia coli and enterotoxigenic Bacteroides fragilis, which induce host DNA double-strand breaks and characteristic mutational signatures; (2) metabolic reprogramming of the intestinal milieu, characterized by an elevation of pro-carcinogenic secondary bile acids (e.g., deoxycholic acid) alongside a depletion of protective short-chain fatty acids, particularly butyrate, thereby activating the Wnt/β-catenin oncogenic pathway; (3) chronic immune microenvironment remodeling, driven by Th17/Treg imbalance and the recruitment of myeloid-derived suppressor cells, which facilitates immune evasion in premalignant niches. Beyond pathogenesis, we critically evaluate the clinical translational value of fecal metagenomic signatures as non-invasive biomarkers for early polyp detection and for predicting post-polypectomy recurrence, noting that microbial resilience after surgery correlates significantly with long-term outcomes. Furthermore, we discuss current evidence for microbiota-targeted interventions, including dietary prebiotics (e.g., resistant starch), probiotic supplementation, and natural bioactive small-molecule compounds (e.g., berberine), which demonstrate chemopreventive potential through modulation of the bile acid enterohepatic circulation and restoration of epithelial barrier integrity. In conclusion, targeting the gut microbiome offers a paradigm shift from the traditional "resect and surveil" approach toward an integrated "resect, restore, and maintain" strategy for colorectal polyp management. However, distinguishing causality from mere correlation across diverse populations and standardizing microbiota-based diagnostic thresholds remains critical challenges for future large-scale prospective validation.***

Keywords: Gut microbiota dysbiosis, Colorectal polyps, Adenoma, Secondary bile acids, Butyrate, Biomarkers, Chemoprevention, Virome, Mycobiome.

1. Pathogenic Mechanisms: How Microbiota Dysbiosis Drives Colorectal Polyp Formation

1.1 Direct Genotoxicity and Host DNA Damage

Accumulating evidence has established that specific genotoxic bacterial strains residing in the dysbiotic gut microbiota can directly inflict DNA damage on colonic epithelial cells, serving as an early "trigger" for polyp initiation. Among these, *pks⁺ Escherichia coli*, which harbors the polyketide synthase (*pks*) genomic island encoding the genotoxin colibactin, has been most extensively characterized [1]. Mechanistically, colibactin induces interstrand crosslinks in host DNA, resulting in double-strand breaks (DSBs) that are detectable as distinct phospho-histone H2AX (γH2AX) foci in colonocytes from patients with sporadic adenomas. Critically, recent whole-genome sequencing analyses of human colorectal adenomas have revealed a unique mutational signature—designated as SBS-*pks*—which serves as a molecular footprint of colibactin exposure, strongly implicating this bacterium in the earliest steps of adenomatous transformation [1]. Parallel to this, enterotoxigenic *Bacteroides fragilis* (ETBF) [2], though not directly genotoxic in terms of DSBs, secretes a zinc-dependent metalloprotease toxin (BFT) that cleaves E-cadherin, disrupting epithelial barrier integrity and activating nuclear β-catenin signaling. Simultaneously, BFT stimulates a pro-inflammatory cascade that generates reactive oxygen species (ROS) within neighboring cells [3], causing oxidative DNA adducts (such as 8-oxo-dG) that further accumulate mutagenic errors [2, 4]. Notably, these two bacterial species are often co-enriched in the mucosal biopsies of high-risk adenoma patients, suggesting a synergistic effect whereby colibactin-driven genomic instability and BFT-mediated junctional disruption converge to create a "permissive mutational field" in the otherwise normal-appearing colonic crypts [5].

1.2 Metabolic Reprogramming of the Intestinal Milieu

Beyond direct bacterial-epithelial contact, gut microbiota profoundly influences polyp formation through the production of a vast array of bioactive metabolites that reshape the intestinal metabolic landscape, with secondary bile acids and short-chain fatty acids (SCFAs) representing the two opposing arms of this regulatory axis.

On the pro-carcinogenic side, a Western-style diet, rich in saturated fats, promotes the expansion of bile acid-metabolizing bacteria [6], such as Lachnoclostridium scindens, which express the 7α-dehydroxylase enzymatic complex [7, 8]. This facilitates the conversion of primary bile

acids (cholic acid and chenodeoxycholic acid) into secondary bile acids, notably deoxycholic acid (DCA) and lithocholic acid (LCA) [9, 10]. At physiologically relevant concentrations observed in the colonic lumen of polyp-forming individuals, DCA acts as a potent tumor promoter by multiple mechanisms: it induces oxidative stress through mitochondrial ROS generation, activates the epidermal growth factor receptor (EGFR) [11], and most importantly, stabilizes β-catenin via phosphorylation inhibition, thereby constitutively activating the Wnt/β-catenin signaling pathway—a hallmark driver of aberrant crypt foci formation [12]. Concurrently, DCA triggers the release of pro-inflammatory cytokines (such as IL-8) from colonic myofibroblasts, amplifying the local inflammatory tone [13].

Conversely, on the protective side, dietary fiber fermentation by saccharolytic bacteria (predominantly Faecalibacterium prausnitzii, Roseburia spp., and Eubacterium spp.) yields butyrate, a SCFA that serves as the primary energy source for colonocytes. In the context of polyp prevention, butyrate exerts its anti-neoplastic effects through two well-characterized pathways: (i) histone deacetylase (HDAC) inhibition, which promotes hyperacetylation of histones and subsequent transcriptional upregulation of cell-cycle arrest genes (e.g., p21^{WAF1/CIP1}), and (ii) activation of G-protein-coupled receptors, particularly GPR43 and GPR109a, which suppress cAMP accumulation and inhibit NF-κB nuclear translocation [14]. Importantly, during dysbiosis, the abundance of butyrate-producing taxa is significantly depleted, leading to a state of "metabolic starvation" and HDAC overactivity in the colonic epithelium, which lowers the apoptotic threshold and allows dysplastic clones to survive and expand. The quantitative balance between DCA and butyrate (the "DCA/butyrate ratio") has thus emerged as a novel composite risk metric, with a high ratio independently correlating with both polyp multiplicity and advanced histological grades [15, 16].

1.3 Immune Microenvironment Remodeling

The third, and perhaps most intricate, pathogenic cascade involves the remodeling of the mucosal immune landscape, where dysbiotic signals are translated into a chronically inflamed microenvironment that nurtures polyp outgrowth [17]. Under homeostatic conditions, the colonic lamina propria maintains a delicate equilibrium between pro-inflammatory Th17 cells and immunosuppressive/regulatory Treg cells [18]. However, in the presence of a dysbiotic microbiome, this equilibrium is profoundly skewed (Figure 1).

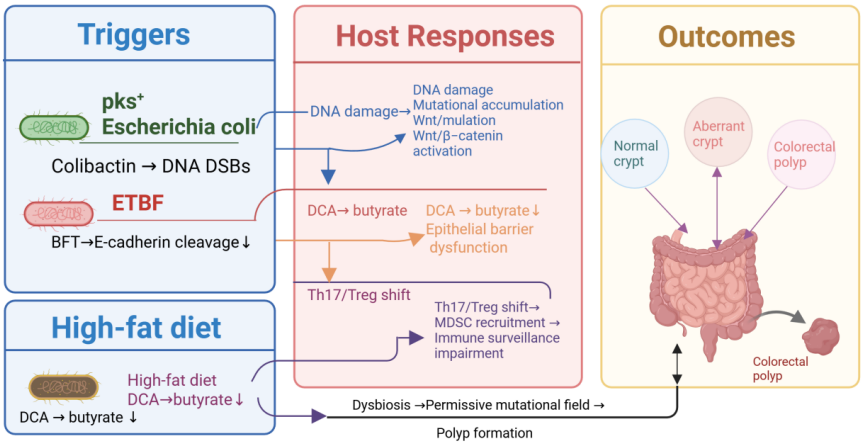

Figure 1: The impact of immune microenvironment remodeling on polyp formation

Specifically, bacterial components (such as lipopolysaccharide from gram-negative bacteria) and metabolites (including DCA) activate Toll-like receptors (TLRs) and the NOD-like receptor family pyrin domain containing 6 (NLRP6) inflammasome on dendritic cells and macrophages [19], which subsequently secrete large amounts of IL-1β and IL-23 [20]. This cytokine milieu drives the expansion and polarization of Th17 cells, which produce IL-17A and IL-22. While these cytokines are protective against extracellular pathogens, their chronic overproduction in the polyp microenvironment exerts detrimental effects: IL-17A enhances the survival of mutant epithelial cells by activating the PI3K/Akt and STAT3 anti-apoptotic pathways [21], while IL-22 promotes epithelial proliferation and stemness via the Wnt/β-catenin axis—essentially providing a "growth boost" to initiated clones [22].

Simultaneously, dysbiosis facilitates the recruitment of myeloid-derived suppressor cells (MDSCs) through the CXCL1-CXCR2 chemokine axis [23, 24]. In patients with large sessile serrated polyps, the proportion of circulating polymorphonuclear MDSCs is significantly elevated [25], and these cells effectively suppress CD8⁺ cytotoxic T lymphocyte activity via arginase-1 (Arg-1) and inducible nitric oxide synthase (iNOS) overproduction [26]. This localized immunosuppressive shielding allows transformed cells to evade immune elimination long before they manifest as endoscopically visible lesions. Furthermore, increased intestinal permeability—a direct consequence of mucus layer thinning and tight junction disruption caused by ETBF and proteolytic bacteria—facilitates the translocation of bacterial products into the submucosa, perpetuating a vicious cycle of "leakiness-inflammation-proliferation" that fundamentally alters the immune vigilance threshold of the polyp-bearing gut [27].

2. Microbiome as a Non-Invasive Biomarker in Polyp Surveillance

2.1 Fecal Metagenomic Signatures for Polyp Detection

Current population-based screening for colorectal polyps relies predominantly on the fecal immunochemical test (FIT),

which, despite its convenience, exhibits limited sensitivity for advanced adenomas (approximately 40%–50%) and performs particularly poorly for sessile serrated lesions (SSLs) [28], which often do not bleed [29]. Consequently, a substantial proportion of high-risk individuals with precursor lesions are falsely reassured by a negative FIT result, leading to missed opportunities for early intervention. In this context, the gut microbiome has emerged as a promising complementary or even alternative non-invasive biomarker pool, given that microbial compositional shifts frequently precede macroscopic polyp formation by months to years.

Contemporary metagenomic studies have adopted two distinct technical routes. The first, 16S rRNA amplicon sequencing [30], offers a cost-effective and high-throughput approach that primarily resolves bacterial taxonomy at the genus level. Through large-scale case-control cohorts, a recurrent dysbiotic signature has been consistently identified in adenoma patients: a significant depletion of saccharolytic genera, including Faecalibacterium, Roseburia, and Blautia, alongside a concurrent enrichment of pro-inflammatory genera such as Bacteroides, Alistipes, and certain members of the Lachnospiraceae family. However, genus-level resolution is inherently limited by functional redundancy, meaning that different bacterial species within the same genus can exert diametrically opposing effects on host physiology [31]. Therefore, the second and more advanced route, shotgun metagenomic sequencing, provides species-level and strain-level taxonomic resolution while simultaneously capturing functional gene modules—such as those encoding polyketide synthases (*pks*), secondary bile acid dehydroxylases (*baiCD*), and butyrate-producing butyryl- CoA transferase (*but*). This functional granularity is clinically meaningful; for instance, the presence of the *pks* genomic island in *E. coli* strains is far more predictive of high-grade dysplasia than the mere abundance of *E. coli* as a species.

To translate these compositional differences into a clinically actionable diagnostic index, researchers have employed machine learning algorithms (including random forest and support vector machines) to construct multi-microbial panels. When validated in independent external cohorts, these panels have demonstrated area under the receiver operating characteristic curve (AUC) values ranging from 0.75 to 0.85 for distinguishing patients with advanced adenomas from healthy controls [32]. Notably, when the microbial panel is combined with FIT, the composite model achieves a marked improvement in sensitivity for SSL detection—from a mere 20% with FIT alone to over 70% with the combinatorial approach—addressing a critical unmet clinical need [33]. Despite these promising results, inter-cohort heterogeneity remains a formidable obstacle: geographic dietary patterns, antibiotic exposure histories, and even stool collection protocols exert profound influences on baseline microbiota composition, necessitating the development of region-specific calibration models prior to widespread clinical deployment.

2.2 Predicting Post-Polypectomy Recurrence

Endoscopic polypectomy, while effective in eradicating visible lesions, does not alter the underlying dysbiotic ecosystem of the host's intestine. Consequently, up to 40% of patients experience metachronous adenoma recurrence within 1 to 3 years following complete resection [34], underscoring the urgent need for a reliable predictor of post-polypectomy outcomes beyond conventional clinical parameters (e.g., age, polyp size, multiplicity, and histological grade). Emerging evidence positions the gut microbiota as a particularly potent prognostic indicator in this post-intervention setting, primarily through two conceptual frameworks: post-resection ecological resilience and baseline recurrence-associated taxa (Figure 2).

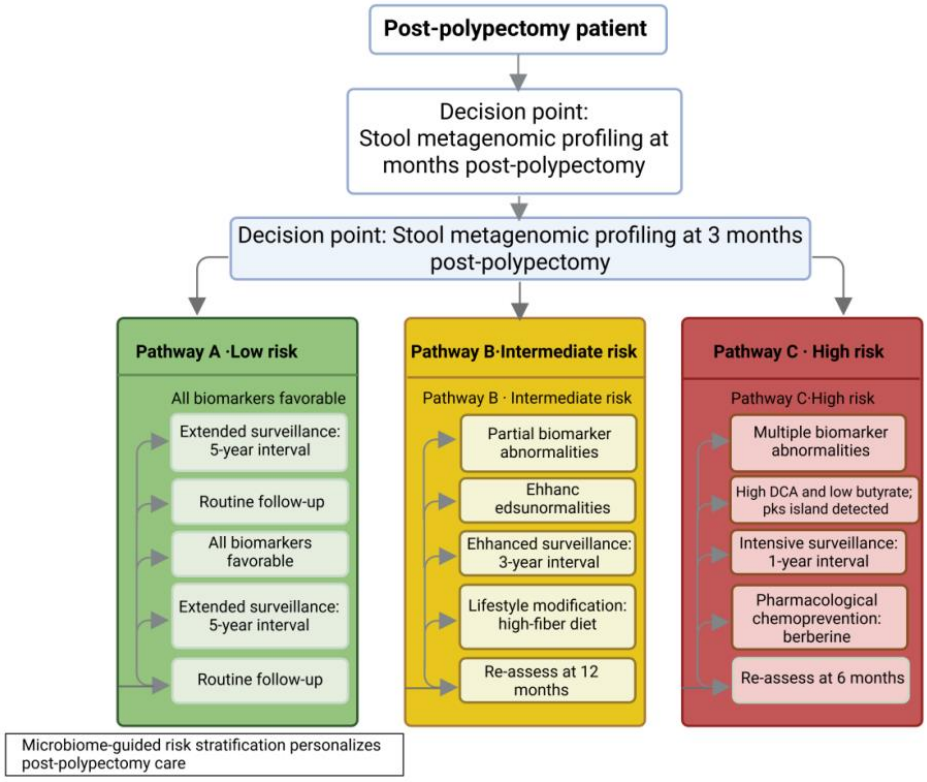

Figure 2: Prediction of recurrence after polypectomy

The concept of ecological resilience refers to the capacity of the gut microbial community to regain its pre-dysbiotic equilibrium after the mechanical disruption of colonoscopy (including bowel preparation) and the mucosal injury of polypectomy. Longitudinal prospective studies have revealed that patients who experience early recurrence exhibit a persistently low microbial α-diversity (Shannon index) as early as 3 months post-polypectomy, accompanied by a failure to restore the abundance of butyrate-producing Clostridium cluster XIVa [35]. Conversely, patients who maintain a recurrence-free status demonstrate rapid recovery of Faecalibacterium prausnitzii abundance within the same timeframe, suggesting that the rate of microbial reconstitution is a dynamic proxy of host gut ecosystem stability. Multivariate Cox regression analyses, adjusting for age and polyp burden, have shown that poor microbial resilience (defined as a post/pre-polypectomy butyrate-producing taxa ratio of <0.6) independently confers a hazard ratio (HR) of approximately 2.5 to 3.0 for 1-year recurrence, a magnitude comparable to or even exceeding that of multiple adenomas (≥3) at baseline [36].

Parallel to resilience dynamics, specific baseline bacterial signatures have been implicated as direct "seeding" agents for recurrence. Patients whose preoperative mucosal biopsies display a persistent enrichment of oral-derived commensals, including Fusobacterium nucleatum and Parvimonas micra, are at a significantly elevated risk of harboring new adenomas at the same or distant anatomical sites during follow-up. The mechanistic underpinning likely involves the capacity of these taxa to colonize post-resection ulcer beds, exploiting the transient breach in epithelial continuity to establish a pro-inflammatory niche that fosters re-initiation of aberrant crypt foci. Furthermore, a high baseline DCA/butyrate ratio—derived from quantitative metabolomic profiling of preoperative stool samples—has been validated as a risk variable, with each unit increase in the log- transformed ratio associated with a 1.5-fold rise in recurrence odds.

From a clinical implementation standpoint, integrating these microbial metrics into a combined clinico-microbial nomogram (incorporating age, polyp histology, baseline microbiota diversity, and DCA/butyrate ratio) has demonstrated improved prognostic accuracy over the conventional ESGE surveillance guidelines alone in recent pilot studies. This evidence strongly advocates for a paradigm shift in surveillance frequency: patients exhibiting favorable microbial profiles could potentially be safely assigned to extended surveillance intervals (e.g., 5 years), whereas those with high-risk microbial signatures might warrant more intensive 6-month or 1-year endoscopic re-evaluation, thereby optimizing the allocation of limited endoscopic resources and minimizing unnecessary procedural burden for low-risk individuals. The identification of high-risk microbial signatures not only refines risk stratification but also opens a therapeutic window: patients with unfavorable profiles may derive particular benefit from microbiota-targeted interventions, which are discussed in the following chapter.

3. Microbiota-Targeted Interventions for Colorectal Polyp Prevention and Recurrence Reduction

Given that dysbiosis is a persistent and modifiable risk factor that remains largely unaddressed by endoscopic polypectomy alone, microbiota-directed strategies have garnered considerable interest as adjunctive or even primary chemopreventive approaches. These interventions operate through three interconnected tiers: (1) dietary modulation of the gut ecosystem, (2) exogenous supplementation with live beneficial microbes, and (3) pharmacological repurposing of small-molecule compounds that exert their anti-neoplastic effects, at least in part, via microbiota-dependent pathways. While preclinical and observational data are robust, it must be acknowledged that high-level evidence from large-scale randomized controlled trials (RCTs) specifically targeting polyp endpoints remains relatively nascent.

3.1 Dietary Patterns and Prebiotic Substrates

Diet is the single most potent determinant of gut microbiota composition over the human lifespan, and epidemiological studies have consistently demonstrated that adherence to a Western-style diet—characterized by high saturated fat and low dietary fiber—shifts the microbial metabolome toward a pro-carcinogenic profile. Conversely, the Mediterranean diet, rich in olive oil, legumes, whole grains, and leafy vegetables, has been associated with a 25%–30% reduction in adenoma recurrence in prospective cohort studies [37, 38], an effect largely mediated by enrichment of *Faecalibacterium prausnitzii* and Roseburia spp. alongside concurrent suppression of secondary bile acid-producing Clostridium cluster XI [39].

Among specific prebiotic substrates, resistant starch (RS) [40]—a form of starch that escapes small intestinal digestion and reaches the colon intact—has emerged as the most mechanistically compelling candidate [41]. Upon fermentation by the colonic saccharolytic microbiota, RS selectively promotes the proliferation of butyrate-producing taxa, particularly Eubacterium rectale and Ruminococcus bromii, resulting in a significant elevation of fecal butyrate concentrations [42, 43]. Several randomized controlled trials have evaluated resistant starch supplementation in adenoma patients, although results have been inconsistent. While the CAPP2 trial in Lynch syndrome carriers showed no effect on adenoma incidence, other studies have reported beneficial effects on intermediate biomarkers such as fecal butyrate concentration [44].Additionally, other fermentable fibers, including inulin and fructo-oligosaccharides (FOS), have shown favorable effects on enhancing intestinal barrier function (via upregulation of tight junction proteins occludin and ZO-1) [45]and reducing luminal IL-1β levels, although their specific impact on polyp recurrence warrants further dedicated investigation [46].

3.2 Probiotics, Synbiotics, and Postbiotics

Probiotic administration offers a more direct approach to augmenting beneficial microbial populations, yet the clinical evidence base for polyp prevention is considerably more nuanced than often portrayed [47]. Several meta-analyses of RCTs using Lactobacillus and Bifidobacterium combination formulas have yielded only modest or non-significant reductions in adenoma recurrence, possibly due to the transient colonization capacity of these exogenous strains,

which typically fail to engraft stably in recipients with a resilient native microbiota [48].

However, strain-specific efficacy has been observed in certain well-designed trials. For instance, Preclinical studies have suggested that Lactobacillus rhamnosus GG (LGG) supplementation may reduce colibactin-producing E. coli colonization, although these findings have not yet been translated into robust clinical evidence for polyp recurrence reduction [49]—suggesting that while intermediate biomarkers improve, hard clinical endpoints require larger sample sizes or longer duration. More promisingly, a specific Bifidobacterium longum BB536 strain demonstrated an ability to suppress the activity of fecal β-glucuronidase—a bacterial enzyme that deconjugates glucuronidated carcinogens and reactivates them in the colonic lumen—thereby lowering the effective exposure dose of genotoxins [50].

The concept of synbiotics (combining probiotics with specific prebiotic substrates) represents a logical evolution aimed at improving the survival and metabolic activity of administered strains. A pilot study investigating a synbiotic formulation in patients with familial adenomatous polyposis (FAP) reported favorable effects on mucosal proliferation markers, although the specific combination of B. longum and FOS requires further validation [51]. Postbiotics, defined as preparations of inanimate microorganisms or their metabolic products (e.g., butyrate enemas, or heat-inactivated Akkermansia muciniphila), avoid the live-engraftment challenge altogether. However, clinical studies specifically focused on colorectal polyps are sparse; currently, this approach remains largely confined to preclinical rodent models of azoxymethane-induced aberrant crypt foci.

3.3 Pharmacological Repurposing: Small-Molecule Compounds with Microbiota-Dependent Chemopreventive Activity

Beyond dietary and live-biotic strategies, several established pharmaceutical agents have garnered renewed attention for their chemopreventive properties, which are increasingly attributed to their capacity to modulate the gut microbial ecosystem and its metabolic output.

Aspirin, the most extensively studied chemopreventive agent for colorectal neoplasia, reduces the risk of recurrent adenomas by approximately 20%–25% in long-term users [52]. Recent mechanistic re-evaluation has revealed that aspirin's anti-adenoma effect is partially abrogated in germ-free or antibiotic-treated mice, indicating a previously unappreciated microbiota-dependent component. Aspirin has been shown to suppress the growth of sulfidogenic bacteria (such as Desulfovibrio spp.) while concurrently promoting the relative abundance of Lactobacillus and Bifidobacterium, thereby attenuating hydrogen sulfide (H_2S)-induced DNA damage and reducing mucosal inflammation. Nonetheless, the clinical application of aspirin for primary polyp prevention remains constrained by its dose-dependent risk of gastrointestinal hemorrhage and peptic ulceration, limiting its widespread use to only the highest-risk subsets of patients (e.g., those with Lynch syndrome or strong family history) [53].

Berberine, an isoquinoline alkaloid derived from the Coptis chinensis plant (classified in Western pharmacology as a natural bioactive small-molecule compound), has attracted substantial interest in gastrointestinal oncology [54]. Unlike conventional antibiotics, berberine exerts a selective bacteriostatic effect against certain pathobionts (particularly Bacteroides and certain Clostridium species) while largely preserving beneficial saccharolytic taxa [55]. Through this modulatory action, berberine profoundly alters the enterohepatic circulation of bile acids. Consequently, in a multicenter RCT involving 1,100 participants with a history of >3 adenomas, a 12-month course of berberine (0.6 g daily) reduced the cumulative adenoma recurrence rate from 36% in the placebo arm to 23% in the treatment arm, a difference that was highly statistically significant ($p<0.001$) [54]. Importantly, whole-genome shotgun sequencing of fecal samples from trial participants revealed that berberine responders exhibited a baseline overabundance of *baiCD*-harboring bacterial genomes, establishing a functional microbiota-based predictive biomarker for treatment efficacy. This "responder stratification" paradigm represents a pioneering step toward precision chemoprevention.

Metformin, a first-line anti-diabetic biguanide, has also demonstrated chemopreventive effects in observational studies of diabetic patients [56]. Beyond its systemic AMPK-activating effects, metformin accumulates in the intestinal lumen at concentrations far exceeding those in the circulation, where it selectively enriches Akkermansia muciniphila—a mucin-degrading commensal that enhances mucus layer thickness and stimulates the production of the anti-inflammatory cytokine IL-10 by colonic macrophages [56]. In a recent small-scale interventional trial in non-diabetic individuals with prior adenomas, metformin (500 mg twice daily) for 6 months significantly reduced the aberrant crypt foci count as assessed by magnifying chromoendoscopy, accompanied by a marked increase in fecal butyrate and a concomitant reduction in fecal DCA [57]. However, the gastrointestinal side-effect profile (diarrhea and bloating) of metformin in non-diabetic populations poses substantial hurdles to its adoption as a general chemopreventive agent, and thus its future use will likely be confined to patients with concomitant insulin resistance or metabolic syndrome.

3.4 Safety Profiles, Indications, and Contraindications

Despite the promising efficacy data discussed above, the clinical adoption of pharmacological chemoprevention for colorectal polyps is critically contingent upon a rigorous risk-benefit assessment. No agent currently meets the criteria for universal primary prophylaxis in average-risk individuals; rather, their use must be meticulously stratified according to baseline cardiovascular risk, metabolic status, and genetic predisposition.

Aspirin remains the most extensively characterized agent, yet its chemopreventive benefit (approximately 20%–25% relative risk reduction for adenoma recurrence) is unequivocally dose-dependent and must be weighed against its well-established hemorrhagic liabilities [58]. In the general population, low-dose aspirin (75–100 mg daily) is associated with a 1.5- to 2.0-fold increased risk of major gastrointestinal

bleeding and a 1.3-fold increased risk of hemorrhagic stroke. Accordingly, current consensus restricts aspirin chemoprophylaxis to high-risk subsets—specifically, individuals with Lynch syndrome, a strong family history of CRC (≥2 first-degree relatives), or those with established cardiovascular comorbidities in whom the anti-thrombotic indication overlaps with chemoprevention. Absolute contraindications include active peptic ulcer disease, prior intracranial hemorrhage, aspirin-exacerbated respiratory disease, and severe hepatic or renal impairment. For eligible patients, concomitant proton pump inhibitor (PPI) co-administration is strongly recommended to mitigate upper gastrointestinal mucosal injury, although emerging data suggest that long-term PPI use may itself adversely affect gut microbiota composition, introducing a secondary modulatory variable that warrants careful monitoring.

Berberine, in contrast, exhibits a considerably more favorable safety profile in the short-to-intermediate term (up to 12 months), with the most frequently reported adverse events being mild and self-limited gastrointestinal symptoms, predominantly constipation (reported in 8%–12% of treated participants) and, less commonly, abdominal bloating and nausea [59]. Notably, constipation is mechanistically linked to berberine's inhibitory effect on intestinal smooth muscle contraction via its weak anti-cholinergic properties, and it typically resolves spontaneously within 2–4 weeks of continued administration or responds to increased dietary fluid intake. Serious adverse events are exceptionally rare, and no significant hepatotoxicity, nephrotoxicity, or myelosuppression has been documented in clinical trial settings. However, pharmacokinetic considerations are paramount: berberine is a potent inhibitor of CYP2D6 and CYP3A4 isoforms and acts as a P-glycoprotein (P-gp) efflux pump modulator [60]. Consequently, it carries a moderate risk of drug-drug interactions with narrow-therapeutic-index substrates (e.g., warfarin, cyclosporine, and certain statins), necessitating either dose adjustment or intensified therapeutic drug monitoring when co-prescribed. Additionally, due to its stimulatory effect on uterine contraction in animal models, berberine is absolutely contraindicated during pregnancy and lactation. From a population-stratification perspective, the aforementioned multicenter RCT data indicate that berberine yields maximal chemopreventive benefit (with an absolute risk reduction of 13% and a corresponding number needed to treat of approximately 8) in patients with a baseline fecal metagenomic signature characterized by high baiCD gene abundance—effectively, those with a "bile-acid-driven" dysbiotic phenotype—suggesting that future clinical implementation should be guided by companion microbial diagnostics rather than prescribed empirically.

Metformin, as a biguanide, is fundamentally a glucose-lowering agent, and its repurposing for polyp prevention is inherently restricted to non-diabetic individuals with concurrent metabolic syndrome features (obesity, insulin resistance, or hypertriglyceridemia), as its chemopreventive effects are partially mediated through systemic AMPK activation that is amplified in hyperinsulinemic states. The major dose-limiting toxicity of metformin in non-diabetic populations is gastrointestinal intolerance—including diarrhea, nausea, and abdominal cramping [61]—which affects 20%–30% of users at the standard 500 mg twice-daily dose, often leading to treatment discontinuation in approximately 5% to 15% of trial participants. To mitigate this, dose titration (starting at 250 mg once daily with gradual escalation over 4 weeks) is mandatory, and the extended-release formulation is strongly preferred over the immediate-release version. Metformin carries a rare but well-documented risk of lactic acidosis (incidence < 0.1 cases per 1,000 patient-years), and therefore remains contraindicated in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², acute unstable congestive heart failure, severe hepatic dysfunction, or a history of metabolic acidosis. For appropriately selected patients with obesity-related adenomas and confirmed insulin resistance, metformin offers the dual advantage of improving metabolic parameters while concurrently modifying the gut ecosystem (Akkermansia enrichment), representing a valuable adjunctive therapy [62].

4. Challenges and Future Perspectives

Despite the compelling evidence linking gut microbiota dysbiosis to colorectal polyp pathogenesis, several formidable obstacles must be overcome before microbiome-based strategies can be seamlessly integrated into routine clinical practice. Concurrently, emerging technological and conceptual advances are opening new avenues that promise to address these very limitations.

4.1 Distinguishing Causality from Correlation: The Pivotal Role of Fecal Microbiota Transplantation

The most fundamental epistemological challenge confronting the field remains the unresolved question of whether observed microbial alterations represent causative drivers or merely secondary passengers that flourish in the microenvironmental niche created by nascent neoplastic lesions. As noted earlier, cross-sectional observational studies—while invaluable for hypothesis generation—are structurally incapable of establishing temporal precedence or formal causation. To elevate associative microbiome data to causal inference, contemporary research has converged upon fecal microbiota transplantation (FMT) in gnotobiotic murine models as the current gold-standard experimental paradigm [63].

In the context of colorectal polyp research, the FMT-based causal validation pipeline operates as follows: human donor microbiota derived from well-phenotyped adenoma patients (or healthy controls) are transferred into germ-free recipient mice, which are subsequently subjected to a conventional colorectal carcinogenesis induction protocol—most commonly the azoxymethane (AOM) / dextran sodium sulfate (DSS) model. [64, 65] The critical experimental readout is whether the recipient animals faithfully recapitulate the donor's polyp phenotype. To date, a series of landmark studies have convincingly demonstrated that germ-free mice colonized with the microbiota from adenoma patients exhibit significantly higher tumor multiplicity and larger polyp burden compared to recipients of healthy-control microbiota, thereby establishing a formal causative transmission of neoplastic susceptibility. Mechanistically, these FMT-based experiments have corroborated that the procarcinogenic effects are not dependent on a single "super-pathogen" but rather on a consortium-level functional shift—notably, the

collective enrichment of the baiCD-driven secondary bile acid biosynthetic pathway and the concurrent depletion of butyrate-producing modules.

Nevertheless, FMT models are not without their own limitations, which must be transparently acknowledged. First, germ-free mice, by definition, lack a native immune-education history, rendering their immunological responses to human microbiota potentially exaggerated or aberrant compared to conventionally colonized animals. Second, the AOM/DSS chemical induction paradigm accelerates carcinogenesis over weeks rather than decades, potentially bypassing the protracted, low-grade inflammatory evolution that characterizes human colorectal polyp progression. Third, the host-specific ecological filters (dietary, metabolic, and immunological) that shape human microbiota composition are poorly replicated in murine recipients, leading to variable engraftment efficiency—a phenomenon known as “colonization resistance.” Recent methodological refinements, including the use of humanized gnotobiotic mice (bearing a human immune system or humanized epithelial receptors) and the adoption of spontaneous polyp models (such as Apc^{Min/+} mice), are beginning to address these limitations. Importantly, bidirectional FMT experiments—transferring “healthy” microbiota into polyp-bearing recipient animals to test for therapeutic reversal — are emerging as a powerful complementary strategy to establish not only causation but also the reversibility of the pathological phenotype.

Beyond rodent models, the human-to-human FMT trial represents the ultimate translational standard for causality and therapeutic proof-of-concept [66]. In oncology, a pioneering phase I trial recently explored the safety and microbiota-engraftment efficacy of FMT from healthy lean donors into patients with obesity-associated adenomas, demonstrating durable colonization of donor-derived butyrate-producing strains and a concomitant reduction in rectal mucosal proliferation marker Ki-67 at 6-month follow-up. Although polyp recurrence reduction was not a primary endpoint in this early-stage study, this approach firmly anchors the causal pathway in human physiology and opens the door to prospective RCTs that assess clinical outcomes. Until such large-scale human FMT intervention trials with hard polyp endpoints are completed, the causal evidence chain, while robust, remains incomplete; future research should therefore prioritize integrating Mendelian randomization analyses using host genetic variants as instrumental variables to further disentangle causality from reverse causation and confounding in large population-based biobanks.Lastly, although FMT serves as a powerful causal tool, its own safety profile in immunocompromised or inflammatory bowel disease populations requires cautious interpretation, as donor-derived pathogen transmission remains a documented albeit rare adverse event (Figure 3).

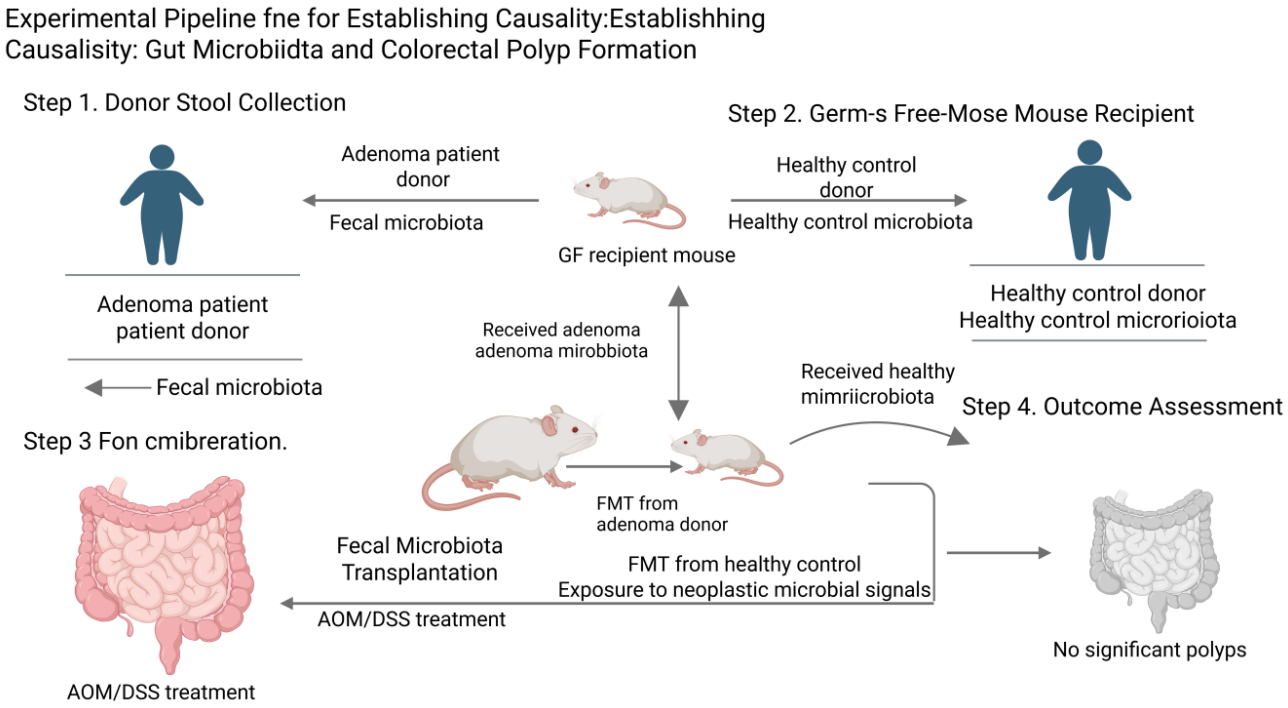

Figure 3: Experimental Pipeline fne for Establishing Causality: Establishhing Causalisity: Gut Microbiidta and Colorectal Polyp Formation

4.2 Standardization and Cross-Cohort Heterogeneity

A second critical bottleneck is the substantial inter-individual and inter-population variability in baseline gut microbiota composition, which is profoundly influenced by geography, ethnicity, habitual diet, medication use (particularly antibiotics and proton pump inhibitors), and even stool sampling and DNA extraction methodologies. Currently, microbiome-based diagnostic panels developed in one geographical region frequently exhibit poor transferability when validated in independent cohorts from different continents, with AUC values often dropping by 0.15–0.25. This lack of generalizability severely undermines the clinical credibility of microbial biomarkers [67]. To overcome this, the field urgently requires universally harmonized protocols for sample collection (including stabilizer solutions and standardized storage temperatures), DNA extraction kits, and bioinformatic pipelines. Additionally, the development of

absolute quantification methods (such as microbe-specific qPCR or flow cytometry) to replace relative abundance data — which are compositional and inherently constrained by the "closed-sum" problem—would significantly improve cross-study comparability. Efforts by international consortia (e.g., the Microbiome Quality Control Project, MBQC) to establish reference standards are underway, but these must be expanded to specifically target colorectal polyp populations.

4.3 Translating High-Dimensional Microbial Data into Clinical Workflows

From a translational perspective, the gap between high-dimensional microbiome data and actionable clinical decision-making remains wide. Most published microbiome studies rely on shotgun metagenomic sequencing, which, while rich in information, remains too costly, time-consuming, and computationally demanding for routine point-of-care application in most healthcare settings. Future clinical deployment will likely pivot away from comprehensive sequencing and toward targeted PCR-based panels that interrogate a curated set of the most robust microbial biomarkers (e.g., *pks* island abundance, *baiCD* gene copy number, and the relative abundance of F. prausnitzii). Such targeted assays could be processed within hours at a fraction of the cost, making them suitable for large-scale screening programs. Furthermore, the integration of microbial data with conventional clinical parameters (age, body mass index, family history) and emerging blood-based biomarkers (e.g., circulating tumor DNA or inflammatory cytokines) into composite machine learning algorithms represents a pragmatic pathway forward, as it leverages the strengths of each modality while compensating for their individual weaknesses. Early proof-of-concept studies have demonstrated that such multi-layer models consistently outperform single-modality classifiers, and prospective validation of these models in real-world endoscopy settings is now eagerly awaited.

4.4 Expanding the Microbial Horizon: The Virome and Mycobiome in Colorectal Polyposis

A notable and scientifically limiting gap in the current literature is its near-exclusive focus on the bacterial component of the gut ecosystem, largely neglecting the viral and fungal communities—collectively termed the virome and mycobiome—which exert potent modulatory influences on bacterial population dynamics and host mucosal immunity. Emerging metagenomic and culturomic evidence, although preliminary, suggests that these non-bacterial kingdoms contribute independently to the polyp-associated ecological shift and warrant dedicated investigation.

The gut virome, predominantly composed of bacteriophages (phages) that infect bacterial hosts, can indirectly shape the colonic microenvironment through predator-prey dynamics. A seminal shotgun metagenomic study profiling the fecal virome of 285 participants (including healthy controls, adenoma patients, and CRC cases) revealed a significant expansion of the Caudovirales order in adenoma patients compared to healthy individuals, with a particularly marked increase in the relative abundance of Phormidium and Synechococcus phages. Quantitative analysis demonstrated that adenoma patients harbored a 2.1-fold higher phage-to-bacterial ratio (the "phage-bactobiome" index) compared to polyp-free controls. Furthermore, the phage-encoded auxiliary metabolic genes (AMGs) in adenoma-associated viromes were enriched for functions related to bacterial central carbon metabolism and lipopolysaccharide biosynthesis, suggesting that phage-mediated metabolic reprogramming of host bacteria may indirectly promote a pro-inflammatory state. More specifically, the abundance of phages targeting butyrate-producing Faecalibacterium prausnitzii was inversely correlated with fecal butyrate concentrations (Spearman's $r = -0.41$, $p<0.01$), providing a mechanistic link between phage expansion and metabolic depletion. These phage-driven dynamics are hypothesised to create a "kill-the-winner" ecological cascade, whereby phages selectively lyse the dominant beneficial saccharolytic bacteria, releasing ecological niches for pathobiont overgrowth [68].

The gut mycobiome, despite being numerically dwarfed by bacteria, exerts disproportionately strong immunological effects via conserved pathogen-associated molecular patterns (PAMPs), particularly β-glucans that activate the host Dectin-1/CARD9 signaling pathway. A large multicenter cohort study employing internal transcribed spacer 2 (ITS2) sequencing of fecal samples from 520 participants demonstrated that adenoma patients exhibited a significant shift in fungal beta-diversity (PERMANOVA $P < 0.001$), characterized by an expansion of opportunistic Candida albicans and a concomitant reduction of Saccharomyces cerevisiae and Malassezia restricta. Notably, the C. albicans relative abundance showed a stepwise increase from healthy controls (0.02% median relative abundance) to low-risk adenomas (0.19%) and further to high-risk advanced adenomas (0.41%, P-trend<0.001). Multivariate logistic regression, adjusting for age, sex, body mass index, and bacterial diversity, identified C. albicans abundance as an independent risk factor for advanced adenoma (OR = 2.31, 95% CI: 1.43–3.72). Mechanistically, C. albicans hyphal forms are known to disrupt epithelial tight junctions via secreted candidalysin, while simultaneously inducing IL-23 and IL-17 production from lamina propria macrophages, synergizing with bacterial Th17-driving signals to amplify local inflammation. Conversely, S. cerevisiae has been proposed as a protective commensal, with its abundance being inversely associated with colonic IL-1β levels and positively correlated with regulatory T-cell frequencies in colonic biopsies [69].

From a diagnostic perspective, combining bacterial, viral, and fungal signatures into a pan-kingdom composite index has demonstrated superior discriminative performance over bacteria-only models. In a proof-of-concept study, the addition of six phage-related and five fungal-related features to a baseline 16S-derived bacterial panel increased the AUC for distinguishing advanced adenomas from healthy controls from 0.78 to 0.87, highlighting the significant and independent additive value of the non-bacterial components. However, mycobiome and virome research faces distinct methodological hurdles: fungal DNA extraction is notoriously inefficient due to resilient cell walls, while virome sequencing suffers from the absence of universal marker genes (unlike 16S for bacteria), necessitating costly and computationally intensive shotgun approaches. Until standardized protocols

for fungal and viral analysis are widely adopted, these findings should be interpreted as hypothesis-generating, yet they unequivocally underscore the incompleteness of any microbiome model that restricts itself exclusively to the bacterial realm. Future mechanistic studies should incorporate murine models colonized with defined bacterial-fungal-phage consortia to delineate the complex inter-kingdom interactions that shape polyp susceptibility (Figure 4).

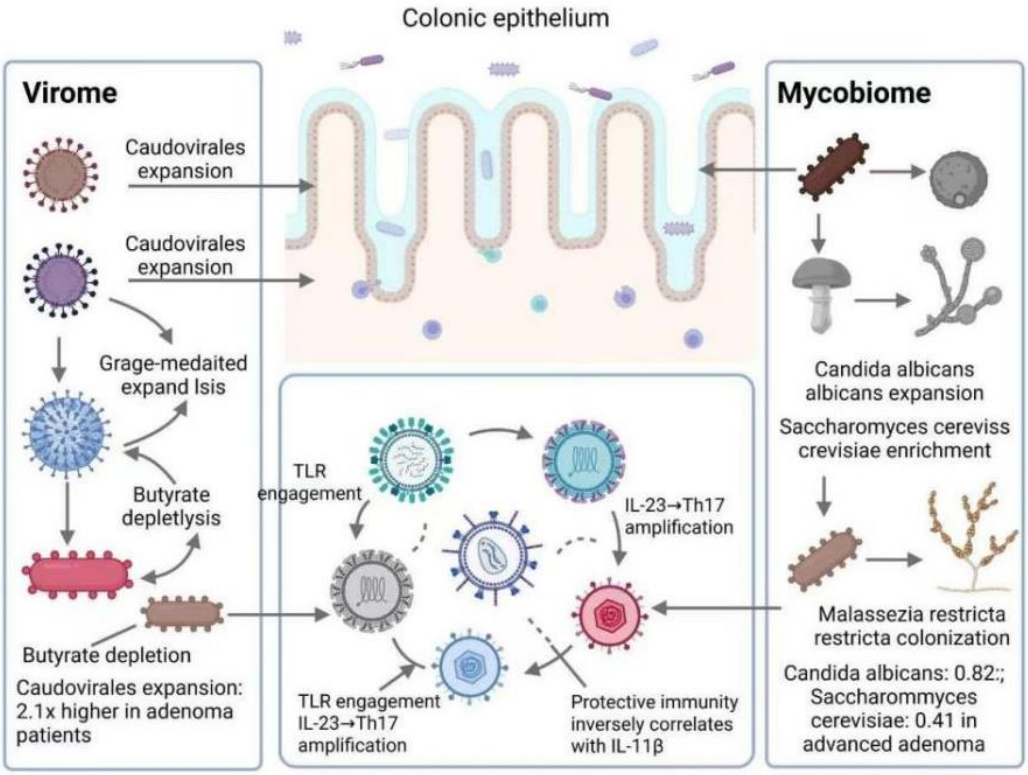

Figure 4: Microorganisms of colonic epithelium

4.5 Towards Microbiome-Guided Personalized Surveillance

The ultimate translational goal is to leverage microbial signatures to individualize post-polypectomy surveillance intervals—a concept that could radically depart from the current "one-size-fits-all" guidelines. As reviewed in Chapter 3, patients with robust microbial resilience and low DCA/butyrate ratios could potentially be assigned to 5-year extended surveillance, while those with persistently hostile microbial profiles might warrant 1-year re-examination. However, achieving this requires rigorous prospective interventional trials that randomly assign patients to either microbiome-guided surveillance or standard guideline-based surveillance, with adenoma recurrence as the pre-specified primary endpoint. Such trials are logistically challenging and require long follow-up periods, but their successful completion would provide the highest level of evidence necessary to effect clinical guideline changes. Additionally, the concept of "microbial resilience training" —intervening with prebiotics or specific dietary regimens immediately post-polypectomy to actively steer the recovering community toward a favorable equilibrium—represents a novel and proactive complementary strategy that warrants systematic investigation in dedicated RCTs.

5. Conclusion

Colorectal polyps, particularly adenomatous and sessile serrated lesions, represent the most important preventable precursors of colorectal cancer, yet their management has long been constrained by a purely anatomical approach that focuses on lesion eradication without addressing the permissive ecological environment in which these lesions arise [70]. The expanding body of evidence reviewed herein establishes gut microbiota dysbiosis as a central, modifiable hub that orchestrates polyp initiation and progression through three interconnected pathogenic cascades: direct genotoxicity inflicted by specific bacterial strains (notably *pks*$^{+}$ *E. coli* and ETBF), metabolic reprogramming of the colonic milieu characterized by a toxic elevation of secondary bile acids (e.g., DCA) alongside a critical depletion of protective butyrate, and chronic remodeling of the mucosal immune microenvironment that favors Th17 polarization and MDSC-mediated immune evasion [71, 72].

Beyond pathogenesis, the clinical translational value of the microbiome is increasingly evident across two complementary dimensions. First, fecal metagenomic signatures offer a promising non-invasive adjunct to FIT for the early detection of advanced adenomas and sessile serrated lesions, with composite panels demonstrating acceptable diagnostic accuracy (AUC 0.75–0.85) and marked improvement in SSL sensitivity when combined with conventional testing. Second, post-polypectomy microbial parameters—particularly ecological resilience and baseline DCA/butyrate ratios—hold significant prognostic value for predicting metachronous recurrence, potentially enabling risk-stratified surveillance that optimizes endoscopic resource allocation [73].

On the interventional front, a spectrum of microbiota-targeted strategies has shown variable but encouraging

chemopreventive potential. Dietary prebiotics, especially resistant starch, reliably augment butyrate production and have demonstrated moderate efficacy in reducing recurrence in high-risk populations. Probiotic supplementation, while mechanistically plausible, has yielded inconsistent results in hard clinical endpoints, likely due to poor engraftment, and thus requires further refinement through synbiotic formulations or postbiotic approaches. More impressively, pharmacological repurposing of natural bioactive small molecules—specifically berberine—has delivered unequivocal positive results in a large-scale multicenter RCT, achieving a clinically meaningful 36% relative reduction in recurrence through targeted suppression of DCA-producing microbial metabolism, exemplifying a successful "drugging the microbiome" paradigm [54].

Nevertheless, significant challenges remain. The field must transcend the correlative nature of current evidence through rigorous longitudinal and gnotobiotic animal studies that establish definitive causality. Universal standardization of pre-analytical and analytical procedures is imperative to overcome cross-cohort heterogeneity and enable clinical validation across diverse populations. Moreover, expanding the analytic scope beyond bacteria to encompass the virome and mycobiome, and embracing multi-omics integration with machine learning, will be essential to capture the full complexity of host–microbe interactions in polyp biology [64].

In conclusion, the traditional "resect and surveil" paradigm is no longer tenable for the comprehensive management of colorectal polyps. The microbiome-centric evidence synthesized in this review strongly advocates for a transformative shift toward an integrated "resect, restore, and maintain" strategy—one that combines precise endoscopic clearance of visible lesions with active ecological restoration of the intestinal microbial ecosystem and long-term maintenance of a butyrate-rich, DCA-depleted, and immune-balanced mucosal environment [74]. As next-generation sequencing technologies become increasingly affordable and targeted microbial assays enter clinical workflows, microbiome-guided personalized prevention and surveillance of colorectal polyps are poised to become a reality within the coming decade, offering a substantive opportunity to reduce the global burden of colorectal cancer at its very earliest and most preventable stage.

References

[1] TERLOUW D, BOOT A, DUCARMON Q R, et al. Enrichment of colibactin-associated mutational signatures in unexplained colorectal polyposis patients [J]. BMC Cancer, 2024, 24(1): 104.

[2] PURCELL R V, PEARSON J, AITCHISON A, et al. Colonization with enterotoxigenic Bacteroides fragilis is associated with early-stage colorectal neoplasia [J]. PLoS One, 2017, 12(2): e0171602.

[3] WONG C C, YU J. Gut microbiota in colorectal cancer development and therapy [J]. Nat Rev Clin Oncol, 2023, 20(7): 429–52.

[4] HWANG S, GWON S Y, KIM M S, et al. Bacteroides fragilis Toxin Induces IL-8 Secretion in HT29/C1 Cells through Disruption of E-cadherin Junctions [J]. Immune Netw, 2013, 13(5): 213–7.

[5] DEJEA C M, FATHI P, CRAIG J M, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria [J]. Science, 2018, 359(6375): 592–7.

[6] O'KEEFE S J. Diet, microorganisms and their metabolites, and colon cancer [J]. Nat Rev Gastroenterol Hepatol, 2016, 13(12): 691–706.

[7] DANIEL S L, RIDLON J M. Clostridium scindens: history and current outlook for a keystone species in the mammalian gut involved in bile acid and steroid metabolism [J]. FEMS Microbiol Rev, 2025, 49.

[8] WAHLSTRöM A, BRUMBAUGH A, SJöLAND W, et al. Production of deoxycholic acid by low-abundant microbial species is associated with impaired glucose metabolism [J]. Nat Commun, 2024, 15(1): 4276.

[9] PAYNE C M, WEBER C, CROWLEY-SKILLICORN C, et al. Deoxycholate induces mitochondrial oxidative stress and activates NF-kappaB through multiple mechanisms in HCT-116 colon epithelial cells [J]. Carcinogenesis, 2007, 28(1): 215–22.

[10] LONGPRE J M, LOO G. Protection of human colon epithelial cells against deoxycholate by rottlerin [J]. Apoptosis, 2008, 13(9): 1162–71.

[11] LIANG H, ESTES M K, ZHANG H, et al. Bile acids target proteolipid nano-assemblies of EGFR and phosphatidic acid in the plasma membrane for stimulation of MAPK signaling [J]. PLoS One, 2018, 13(8): e0198983.

[12] LIU Y, YIN J, LU L, et al. The role of deoxycholic acid in macrophage polarization and remodeling of the tumor microenvironment during colorectal adenoma-carcinoma transition [J]. Cancer Metab, 2025, 13(1): 47.

[13] LIU B, HUANG Y, WANG X, et al. Butyrate blocks cell cycle progression in colorectal cancer organoids partially through HDAC2 inhibition [J]. Front Immunol, 2026, 17: 1788434.

[14] THANGARAJU M, CRESCI G A, LIU K, et al. GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon [J]. Cancer Res, 2009, 69(7): 2826–32.

[15] REBERSEK M. Gut microbiome and its role in colorectal cancer [J]. BMC Cancer, 2021, 21(1): 1325.

[16] LOUCA P, MANNING S, HACKNEY E, et al. Gut microbiome signatures in colorectal neoplasia: a cross-sectional study across neoplasia stages and subtypes [J]. Gut, 2026.

[17] TSE B C Y, WELHAM Z, ENGEL A F, et al. Genomic, Microbial and Immunological Microenvironment of Colorectal Polyps [J]. Cancers (Basel), 2021, 13(14).

[18] ELSAYED I, LI L, SHEAHAN K, et al. Adenoma to carcinoma: A portrait of molecular and immunological profiles of colorectal sporadic tumors [J]. Int Immunopharmacol, 2021, 100: 108168.

[19] CHEN G Y, LIU M, WANG F, et al. A functional role for Nlrp6 in intestinal inflammation and tumorigenesis [J]. J Immunol, 2011, 186(12): 7187–94.

[20] CUI G, YUAN A, PANG Z, et al. Differential profile of protumor immunological factors between the tumor site and the tumor-free site - predictive potential of IL-8 and

COX2 for colorectal cancer and metastasis [J]. Int Immunopharmacol, 2023, 118: 110089.
[21] CUI G, WANG Z, LIU H, et al. Cytokine-mediated crosstalk between cancer stem cells and their inflammatory niche from the colorectal precancerous adenoma stage to the cancerous stage: Mechanisms and clinical implications [J]. Front Immunol, 2022, 13: 1057181.
[22] HUBER S, GAGLIANI N, ZENEWICZ L A, et al. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine [J]. Nature, 2012, 491(7423): 259–63.
[23] CHUN E, LAVOIE S, MICHAUD M, et al. CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function [J]. Cell Rep, 2015, 12(2): 244–57.
[24] PAN J, ZHAO L, DU H, et al. Cannabidiol suppresses emergency MDSCs generation by disturbing EEF1B2-mediated C/EBPβ protein synthesis in colorectal adenomas [J]. J Immunother Cancer, 2026, 14(1).
[25] MA P, BEATTY P L, MCKOLANIS J, et al. Circulating Myeloid Derived Suppressor Cells (MDSC) That Accumulate in Premalignancy Share Phenotypic and Functional Characteristics With MDSC in Cancer [J]. Front Immunol, 2019, 10: 1401.
[26] DUFAIT I, SCHWARZE J K, LIECHTENSTEIN T, et al. Ex vivo generation of myeloid-derived suppressor cells that model the tumor immunosuppressive environment in colorectal cancer [J]. Oncotarget, 2015, 6(14): 12369–82.
[27] YU S, WANG X, LI Z, et al. Solobacterium moorei promotes the progression of adenomatous polyps by causing inflammation and disrupting the intestinal barrier [J]. J Transl Med, 2024, 22(1): 169.
[28] IMPERIALE T F, GRUBER R N, STUMP T E, et al. Performance Characteristics of Fecal Immunochemical Tests for Colorectal Cancer and Advanced Adenomatous Polyps: A Systematic Review and Meta-analysis [J]. Ann Intern Med, 2019, 170(5): 319–29.
[29] CHANG L C, SHUN C T, HSU W F, et al. Fecal Immunochemical Test Detects Sessile Serrated Adenomas and Polyps With a Low Level of Sensitivity [J]. Clin Gastroenterol Hepatol, 2017, 15(6): 872–9.e1.
[30] SHEN X J, RAWLS J F, RANDALL T, et al. Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas [J]. Gut Microbes, 2010, 1(3): 138–47.
[31] LOUIS P, FLINT H J. Formation of propionate and butyrate by the human colonic microbiota [J]. Environ Microbiol, 2017, 19(1): 29–41.
[32] ZHOU D, CHEN Y, WANG Z, et al. Integrating clinical and cross-cohort metagenomic features: a stable and non-invasive colorectal cancer and adenoma diagnostic model [J]. Front Mol Biosci, 2023, 10: 1298679.
[33] BAXTER N T, RUFFIN M T T, ROGERS M A, et al. Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions [J]. Genome Med, 2016, 8(1): 37.
[34] SHI X, YANG Z, WU Q, et al. Colorectal adenoma recurrence rates among post-polypectomy patients in the placebo-controlled groups of randomized clinical trials: a meta-analysis [J]. Oncotarget, 2017, 8(37): 62371–81.
[35] BYRD D A, VOGTMANN E, ORTEGA-VILLA A M, et al. Prospective and Cross-sectional Associations of the Rectal Tissue Microbiome with Colorectal Adenoma Recurrence [J]. Cancer Epidemiol Biomarkers Prev, 2023, 32(3): 435–43.
[36] LIANG J Q, ZENG Y, KWOK G, et al. Novel microbiome signatures for non-invasive diagnosis of adenoma recurrence after colonoscopic polypectomy [J]. Aliment Pharmacol Ther, 2022, 55(7): 847–55.
[37] HASLAM A, ROBB S W, HéBERT J R, et al. Greater adherence to a Mediterranean diet is associated with lower prevalence of colorectal adenomas in men of all races [J]. Nutr Res, 2017, 48: 76–84.
[38] COTTET V, BONITHON-KOPP C, KRONBORG O, et al. Dietary patterns and the risk of colorectal adenoma recurrence in a European intervention trial [J]. Eur J Cancer Prev, 2005, 14(1): 21–9.
[39] APRILE F, BRUNO G, PALMA R, et al. Microbiota Alterations in Precancerous Colon Lesions: A Systematic Review [J]. Cancers (Basel), 2021, 13(12).
[40] VITAL M, HOWE A, BERGERON N, et al. Metagenomic Insights into the Degradation of Resistant Starch by Human Gut Microbiota [J]. Appl Environ Microbiol, 2018, 84(23).
[41] WATSON K M, SIEMENS K N, ANAND S, et al. Dietary and lifestyle associations with microbiome diversity [J]. Gut Pathog, 2022, 14(1): 49.
[42] SAETANG J, SANGKHATHAT S. Diets link metabolic syndrome and colorectal cancer development (Review) [J]. Oncol Rep, 2017, 37(3): 1312–20.
[43] RANGARAJAN A A, CHIA H E, AZALDEGUI C A, et al. Ruminococcus bromii enables the growth of proximal Bacteroides thetaiotaomicron by releasing glucose during starch degradation [J]. Microbiology (Reading), 2022, 168(4).
[44] LI H, ZHANG L, LI J, et al. Resistant starch intake facilitates weight loss in humans by reshaping the gut microbiota [J]. Nat Metab, 2024, 6(3): 578–97.
[45] WU R Y, ABDULLAH M, MääTTäNEN P, et al. Protein kinase C δ signaling is required for dietary prebiotic-induced strengthening of intestinal epithelial barrier function [J]. Sci Rep, 2017, 7: 40820.
[46] LI X, JIANG B, GAO T, et al. Effects of inulin on intestinal flora and metabolism-related indicators in obese polycystic ovary syndrome patients [J]. Eur J Med Res, 2024, 29(1): 443.
[47] KAN H X, CAO Y, MA Y, et al. Efficacy and safety of probiotics, prebiotics, and synbiotics for the prevention of colorectal cancer and precancerous lesion in high-risk populations: A systematic review and meta-analysis of randomized controlled trials [J]. J Dig Dis, 2024, 25(1): 14–26.
[48] ALANDER M, SATOKARI R, KORPELA R, et al. Persistence of colonization of human colonic mucosa by a probiotic strain, Lactobacillus rhamnosus GG, after oral consumption [J]. Appl Environ Microbiol, 1999, 65(1): 351–4.
[49] SARSHAR M, SCRIBANO D, MARAZZATO M, et al. Genetic diversity, phylogroup distribution and virulence gene profile of pks positive Escherichia coli colonizing

human intestinal polyps [J]. Microb Pathog, 2017, 112: 274–8.
[50] KULKARNI N, REDDY B S. Inhibitory effect of Bifidobacterium longum cultures on the azoxymethane-induced aberrant crypt foci formation and fecal bacterial beta-glucuronidase [J]. Proc Soc Exp Biol Med, 1994, 207(3): 278–83.
[51] SALMINEN S, COLLADO M C, ENDO A, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics [J]. Nat Rev Gastroenterol Hepatol, 2021, 18(9): 649–67.
[52] ZHAO T Y, TU J, WANG Y, et al. The Efficacy of Aspirin in Preventing the Recurrence of Colorectal Adenoma: a Renewed Meta-Analysis of Randomized Trials [J]. Asian Pac J Cancer Prev, 2016, 17(5): 2711–7.
[53] ZHAO R, COKER O O, WU J, et al. Aspirin Reduces Colorectal Tumor Development in Mice and Gut Microbes Reduce its Bioavailability and Chemopreventive Effects [J]. Gastroenterology, 2020, 159(3): 969–83.e4.
[54] CHEN Y X, GAO Q Y, ZOU T H, et al. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study [J]. Lancet Gastroenterol Hepatol, 2020, 5(3): 267–75.
[55] WOLF P G, DEVENDRAN S, DODEN H L, et al. Berberine alters gut microbial function through modulation of bile acids [J]. BMC Microbiol, 2021, 21(1): 24.
[56] JONES G R, MOLLOY M P. Metformin, Microbiome and Protection Against Colorectal Cancer [J]. Dig Dis Sci, 2021, 66(5): 1409–14.
[57] HIGURASHI T, TAKAHASHI H, ENDO H, et al. Metformin efficacy and safety for colorectal polyps: a double-blind randomized controlled trial [J]. BMC Cancer, 2012, 12: 118.
[58] LANAS A, WU P, MEDIN J, et al. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis [J]. Clin Gastroenterol Hepatol, 2011, 9(9): 762–8.e6.
[59] LI Z, WANG Y, XU Q, et al. Berberine and health outcomes: An umbrella review [J]. Phytother Res, 2023, 37(5): 2051–66.
[60] BATHAEI P, IMENSHAHIDI M, HOSSEINZADEH H. Effects of Berberis vulgaris, and its active constituent berberine on cytochrome P450: a review [J]. Naunyn Schmiedebergs Arch Pharmacol, 2025, 398(1): 179–202.
[61] SZYMCZAK-PAJOR I, DRZEWOSKI J, WENCLEWSKA S, et al. Metformin-Associated Gastrointestinal Adverse Events Are Reduced by Probiotics: A Meta-Analysis [J]. Pharmaceuticals (Basel), 2024, 17(7).
[62] SILVERII G A. Optimizing metformin therapy in practice: Tailoring therapy in specific patient groups to improve tolerability, efficacy and outcomes [J]. Diabetes Obes Metab, 2024, 26 Suppl 3: 42–54.
[63] JULIEN TAP A A, VéRONIQUE JARROUSSE, SANDRA GUILMEAU, JEANNE TRAN, VANNHIEU P L, THIERRY PEDRON, JEAN-PIERRE FURET, ANDRé BADO, IRADJ, SOBHANI. Early Phenotypical Changes Induced By Transfer Of Human Fecal Microbiota from Colorectal Cancer Patients To Germ-Free Mice [J]. 2022.
[64] WONG S H, ZHAO L, ZHANG X, et al. Gavage of Fecal Samples From Patients With Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-Free and Conventional Mice [J]. Gastroenterology, 2017, 153(6): 1621–33.e6.
[65] SONG Q, GAO Y, LIU K, et al. Gut microbial and metabolomics profiles reveal the potential mechanism of fecal microbiota transplantation in modulating the progression of colitis-associated colorectal cancer in mice [J]. J Transl Med, 2024, 22(1): 1028.
[66] YU H, LI X X, HAN X, et al. Fecal microbiota transplantation inhibits colorectal cancer progression: Reversing intestinal microbial dysbiosis to enhance anti-cancer immune responses [J]. Front Microbiol, 2023, 14: 1126808.
[67] THOMAS A M, MANGHI P, ASNICAR F, et al. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation [J]. Nat Med, 2019, 25(4): 667–78.
[68] ZHANG P, TUO X, JIANG J, et al. Characteristics of the gut virome in patients with premalignant colorectal adenoma [J]. J Transl Med, 2025, 23(1): 597.
[69] SO S H S, JIANG W, LI Y, et al. Mucosal DNA and RNA virome alterations and their interactions with human RNA and microRNA transcriptomes in colorectal polyps [J]. eGastroenterology, 2025, 3(3): e100194.
[70] JIAQUN H, JING Z, YUNFENG Y, et al. Comprehensive evaluation and progress of colorectal cancer screening methods [J]. Gut Pathog, 2025, 17(1): 73.
[71] VALCIUKIENE J, STRUPAS K, POSKUS T. Tissue vs. Fecal-Derived Bacterial Dysbiosis in Precancerous Colorectal Lesions: A Systematic Review [J]. Cancers (Basel), 2023, 15(5).
[72] SADEGHI M, MESTIVIER D, SOBHANI I. Contribution of pks+ Escherichia coli (E. coli) to Colon Carcinogenesis [J]. Microorganisms, 2024, 12(6).
[73] CHEN F, LI S, GUO R, et al. Meta-analysis of fecal viromes demonstrates high diagnostic potential of the gut viral signatures for colorectal cancer and adenoma risk assessment [J]. J Adv Res, 2023, 49: 103–14.
[74] HUANG J, CHEN Z, WANG M, et al. Efficacy and safety of fecal microbiota transplantation in reducing recurrence of colorectal adenomas after endoscopic resection: study protocol for a multicenter, open-label, randomized, no-treatment-controlled trial [J]. Trials, 2026, 27(1).