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Microbial and Molecular Drivers of early-Onset Colorectal Cancer

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Abstract: Global incidence of early-onset colorectal cancer (EO-CRC) has increased by approximately 2% annually over the past three decades, representing a fundamental shift in the epidemiology of colorectal cancer (CRC). EO-CRC, defined as a diagnosis before the age of 50, now accounts for approximately 10–12% of all new CRC cases, while incidence rates in older populations have stabilized or declined. This narrative review compares the molecular, genetic, epigenetic, and microbial landscapes of EO-CRC and late onset colorectal cancer (LO-CRC) through synthesis of the available evidence. We highlight growing evidence that EO-CRC may not be just an early manifestation of sporadic disease but rather a heterogeneous malignancy with distinct molecular signatures by combining data from recent multi-omics studies and large-scale genomic consortia such as TCGA and GECCO. Notably, emerging multi-omics evidence highlights a distinct microbiome signature in EO-CRC, with enrichment of *Flavonifractor plautii* and genotoxic pks+ (polyketide synthase-positive) *Escherichia coli*, which may contribute to early carcinogenesis through flavonoid depletion, immune modulation, and colibactin-mediated DNA damage. These molecular and microbial features correlate clinically with a left-sided anatomical predominance, advanced stage at diagnosis, and aggressive histopathological characteristics, including mucinous and signet ring cell differentiation, particularly in patients under 35

years. These findings have important clinical implications for age-stratified screening, biomarker-guided risk assessment, and the development of targeted therapeutic strategies tailored to younger CRC patients. This review highlights critical gaps related to missing heritability and proposes a precision oncology framework for age-stratified screening and biomarker directed therapy. Addressing the unmet clinical need for earlier detection strategies tailored to younger populations remains a central priority for reducing the growing public health burden of this disease. Although hereditary syndromes such as Lynch syndrome are enriched among younger patients (16–25%), the majority of EO-CRC cases are sporadic and exhibit a predominantly microsatellite stable (MSS), low tumour mutational burden (TMB) phenotype, suggesting distinct non-hereditary molecular and environmental drivers. Transcriptomic analyses demonstrate a marked enrichment of the CMS2 subtype in EO-CRC (~75%) compared to LO-CRC (~40%), reflecting dominant activation of canonical Wnt/MYC signalling pathways. Somatically, the mutational landscape of EO-CRC may exhibit a distinct hierarchy of driver mutations, with an increased frequency of TP53 and CTNNB1 mutations and a reduced frequency of BRAF V600E and APC mutations compared with older patients. Epigenetically, young tumours have been reported to present with more extensive global hypomethylation, especially of LINE-1 elements, and more pronounced methylation canyon erosion, compared with the CpG Island Methylator Phenotype (CIMP-High) commonly observed in right-sided tumours of older patients.

Keywords: Colorectal Cancer, Molecular, Multi-Omics, EO-CRC, LO-CRC, Microbiome

1. Introduction

1.1. The Global Burden of Early-Onset Disease

Colorectal cancer has traditionally been viewed as a disease predominantly associated with aging resulting from the gradual accumulation of somatic mutations over several decades [1]. Consequently, screening protocols and risk-assessment models were therefore historically designed for individuals aged 50 years and older. However, epidemiological trends over the past thirty years have identified a significant and consistent shift. While CRC incidence in adults over 50 has declined, a trend largely credited to the identification and excision of precancerous adenomas during screening colonoscopies, the incidence in individuals under 50 has increased globally by roughly 2% annually [2].

While improved detection may contribute modestly, epidemiological evidence indicates that this trend reflects a true increase in disease incidence. The distal colon and

rectum are where this rise is most noticeable. The incidence of rectal cancer among young adults has increased fourfold since individuals born circa 1950 [3]. The unusual course of early onset colorectal cancer (EO-CRC) suggests that there are certain causes behind it. Unlike late-onset colorectal cancer (LO-CRC), primarily associated with aging and the cumulative effects of sporadic mutations, early-onset colorectal cancer (EO-CRC) is increasingly acknowledged as a phenomenon linked to specific birth cohorts. Individuals born post-1950 exhibit an elevated risk of colorectal cancer (CRC) that remains constant with advancing age [4]. This pattern suggests that environmental exposures during crucial early life stages, from conception to adolescence, may play a substantial role in early carcinogenesis.

1.2. The Exposome and Early Carcinogenesis

The exposome is the total of all the environmental factors that affect a person over their lifetime. For the generations most affected by the EO-CRC epidemic, this means big changes in how they eat, like eating more ultra-processed foods and high-fructose corn syrup, being less active, having higher rates of obesity, and using antibiotics a lot as kids. These factors do not act independently but interact with the host genome and the developing gut microbiome through specific gene environment interactions. For example, obesity-associated hyperinsulinemia may activate the IGF-1/PI3K/AKT signaling pathway, enhancing cellular proliferation in genetically susceptible individuals, while antibiotic-induced dysbiosis may promote colonization by genotoxic bacteria such as pks+ *Escherichia coli*, leading to DNA damage via colibactin-mediated mutagenesis [5, 6]. Additionally, chronic inflammatory states linked to diet and microbiome alterations may interact with host immune regulatory pathways, further facilitating early tumorigenesis [7–9].

It is thought that the interaction between the exposome and the genome makes it easier for cells to become cancerous. The traditional adenoma carcinoma sequence in LO-CRC generally spans 10 to 15 years; however, this duration seems to be expedited in EO-CRC [10]. The biological severity of the disease, which often shows up at Stage III or IV, suggests that tumors in younger people may either skip the extended adenoma phase or move through it quickly through chromosomal instability (CIN) pathways instead of the microsatellite instability (MSI) pathways that are more common in older people [11, 12]. These epidemiological and environmental observations collectively suggest that EO-CRC may arise through partially distinct biological pathways compared with conventional age-associated CRC. Consequently, increasing research efforts have focused on defining the unique molecular, epigenetic, transcriptomic, and microbial features underlying EO-CRC

pathogenesis, with the goal of improving risk stratification, early detection, and precision therapeutic approaches.

1.3. Clinical Distinctiveness

Clinically, patients with EO-CRC frequently present with a distinct clinical profile. They often have to wait longer for a diagnosis, with a median time of about 128 days compared to 79 days for LO-CRC [13]. There are many reasons for this delay, but one of the main ones is that younger patients often have a low index of clinical suspicion when they show symptoms that are often ignored, like abdominal pain or haematochezia. The disease's anatomical distribution is also interesting. EO-CRC is mostly found in the distal colon and rectum, while LO-CRC is more evenly spread out or limited to the proximal colon [14]. This anatomical preference is a major sign of a different molecular pathogenesis, especially since the proximal and distal colon come from different embryological sources and have different vascular and neural features. Importantly, increasing evidence suggests that delayed diagnosis remains one of the major contributors to adverse outcomes in EO-CRC. Younger patients are frequently evaluated initially for benign gastrointestinal conditions, resulting in repeated healthcare encounters before colonoscopy investigation is performed. This diagnostic delay may contribute to the higher frequency of advanced-stage presentation observed in EO-CRC cohorts [15]. Consequently, improving clinician awareness regarding persistent rectal bleeding, unexplained iron deficiency anemia, altered bowel habits, and abdominal pain in younger adults is critical to facilitate earlier detection and timely referral for colonoscopy evaluation [16]. Key epidemiological and clinical differences between EO-CRC and LO-CRC are summarized in Table 1. Younger patients are also disproportionately misdiagnosed with benign conditions such as haemorrhoids or irritable bowel syndrome prior to a correct diagnosis, a pattern that further compounds diagnostic delay. The broader economic and psychosocial impact of this diagnostic delay on younger patients and their families remains comparatively understudied and warrants dedicated investigation.

1.4. Scope and Methodology of the Review

Given the narrative nature of this review, formal systematic review procedures and quantitative study selection criteria were not applied; emphasis was instead placed on studies providing significant biological, translational, and clinical insights into EO-CRC. This narrative review was developed through a comprehensive literature search of PubMed, Web of Science, and Scopus databases for articles published between January 2015 and March 2026. Search terms included combinations of “early-onset colorectal cancer,” “young-onset colorectal cancer,” “EO-CRC,” “molecular subtypes,” “germline predisposition,” “tumor

mutational burden," "epigenetics," "microbiome," "metabolomics," and "precision medicine." Priority was given to large cohort studies, systematic reviews, meta-analyses, genomic and multi-omics investigations, and mechanistic studies relevant to the molecular biology and pathogenesis of EO-CRC. Additional articles were identified through manual screening of reference lists from key publications.

Table 1. Epidemiological Differences Between EO-CRC and LO-CRC.

Feature	EO-CRC	LO-CRC
Incidence Trend	Increasing globally (~2% annually)	Stable or declining in screened populations
Typical Age	<50 years (distinct subgroup <35 years)	≥50 years
Anatomical Distribution	Predominantly distal colon and rectum	More proximal/right-sided distribution
Stage at Diagnosis	Frequently advanced (Stage III/IV)	More commonly detected earlier through screening
Hereditary Contribution	Higher (16–25%)	Lower (~5%)
Sex Distribution	Rising incidence reported in both sexes; some cohorts show increasing rectal cancer burden in younger women	Slight male predominance overall
Geographic Trends	Rapid increases in Westernized and urbanized populations	Globally prevalent but decreasing in screened regions
Major Contributing Factors	Exposome, obesity, microbiome dysbiosis, hereditary predisposition	Aging, cumulative somatic mutations, lifestyle factors

2. Germline Predisposition: The Hereditary Component

One of the clearest distinctions between EO-CRC and LO-CRC is the contribution of hereditary cancer syndromes. Somatic aging is the main cause of most LO-CRC, but germline variants play a substantially larger role in younger patients.

2.1. Prevalence of Pathogenic Germline Variants

In the past, it was thought that EO-CRC was mostly a genetic disease. Recent data clarifies this perspective: germline mutations represent approximately 5% of LO-CRC cases, yet are found in 16 to 25% of EO-CRC patients [17]. This signifies a substantial enrichment; however, it also underscores that 75 to 84% of EO-CRC cases are sporadic, devoid of a recognized high penetrance germline driver. Even so, the high number of hereditary syndromes means that all CRC patients under 50 should get universal germline multigene panel testing. This is now a requirement in NCCN and ESMO guidelines [18]. From a clinical perspective, current guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommend universal tumor screening for mismatch repair (MMR) deficiency in all newly diagnosed colorectal cancer cases, regardless of age. This is typically performed using immunohistochemistry (IHC) for MMR proteins or microsatellite instability (MSI) testing [19]. In parallel, germline multigene panel testing is strongly recommended for all patients diagnosed under the age of 50, given the high prevalence of pathogenic variants in this population. For older patients, age-directed and family history-based approaches remain relevant; however, increasing evidence supports broader testing strategies due to the limitations of clinical criteria alone. Reflex testing workflows, incorporating BRAF V600E mutation or MLH1 promoter methylation analysis in MLH1-deficient tumor's, are essential to distinguish sporadic from hereditary cases [20].

2.2. Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer)

Lynch Syndrome (LS) is the most common hereditary cause of EO-CRC, caused by pathogenic loss of function variants in DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, or deletions in *EPCAM* [21]. Regarding differential diagnosis, a critical distinction must be made between MSI-High (MSI-H) phenotypes in EO-CRC versus LO-CRC. In older adults, MSI-H is common (~15%) and typically sporadic, caused by the epigenetic hypermethylation of the *MLH1* promoter, which is associated with the CIMP-High phenotype and *BRAF* V600E mutations. In contrast, MSI-H in EO-CRC is relatively rare, occurring in approximately 10 to 30% of cases, but it is highly predictive of Lynch Syndrome [22]. Sporadic *MLH1* hypermethylation is virtually non-existent in patients under 35; therefore, the presence of MSI-H in a young patient strongly suggests Lynch syndrome and warrants prompt confirmatory germline testing, although rare cases of sporadic MLH1 hypermethylation may still occur [23]. On the other hand, genotype phenotype correlations also show that the specific gene mutated influences the age of onset. *MLH1* and *MSH2* carriers typically present at younger ages, often before age 45, whereas *MSH6* and *PMS2* carriers may present later, sometimes blurring the line between early and average onset [24].

When a germline pathogenic variant is identified in a patient with EO-CRC, cascade testing should be offered to at-risk relatives, as this enables preventive surveillance and earlier cancer detection within the family.

2.3. Polyposis Syndromes

Familial Adenomatous Polyposis (FAP) is caused by germline mutations in the *APC* gene. Classic FAP presents with hundreds of polyps in adolescence, leading to a near 100% cancer risk by the age of 40 if untreated. However, Attenuated FAP (AFAP), caused by mutations at the 5' or 3' ends of the *APC* gene, presents with fewer than 100 polyps and a later onset, often in the 30s to 50s, frequently mimicking sporadic EO-CRC [25]. Additionally, MUTYH Associated Polyposis (MAP) is a recessive syndrome caused by biallelic mutations in the *MUTYH* base excision repair gene. Patients often present with a phenotype similar to AFAP or even solitary cancers in their 40s. Current guidelines emphasize testing for *MUTYH* in all EO-CRC patients, even in the absence of a florid polyposis phenotype [26].

2.4. The Missing Heritability Conundrum

A major gap in current knowledge is the missing heritability of EO-CRC. Approximately 20 to 30 percent of EO-CRC patients exhibit a strong familial clustering of cancer, characterized by a family history of CRC in a first degree relative, but test negative for known syndromes like LS or FAP [27]. This group, sometimes referred to as Familial Colorectal Cancer Type X, likely harbours undiscovered moderate penetrance variants or distinct polygenic risk profiles.

2.4.1. Novel candidate genes

Recent whole exome sequencing (WES) and genome wide association studies (GWAS) have begun to identify novel susceptibility loci. For example, a 2024 study identified *MEIKIN* as a novel susceptibility gene [28]. Loss of function variants in *MEIKIN*, a gene involved in kinetochore assembly and meiosis, were enriched in EO-CRC cohorts. This suggests a mechanism of chromosomal instability (CIN) driven by meiotic or mitotic errors, which is distinct from the MMR defects of Lynch Syndrome. Furthermore, variants regulating *POLA2* expression have been implicated in early oncogenesis [29]. *POLA2* encodes a subunit of DNA Polymerase Alpha, which is critical for DNA replication initiation. Its dysregulation may accelerate somatic mutation accumulation in the rapidly dividing colonic crypts of young individuals. Finally, germline mutations in the exonuclease domains of *POLE* and *POLD1* cause Polymerase Proofreading Associated Polyposis (PPAP) [30]. These tumors are ultra-hypermutated but microsatellite stable (MSS), a unique phenotype that can drive cancer in the 30s or 40s. Although rare, they represent a distinct molecular subclass

responsive to immunotherapy. These findings remain preliminary and require validation in larger independent and ethnically diverse cohorts before their biological and clinical significance can be fully established

2.4.2. Polygenic risk scores (PRS)

Growing evidence suggests that sporadic EO-CRC may partly arise from the cumulative effect of multiple common, low-penetrance single nucleotide polymorphisms (SNPs) [31]. Genome-wide association studies (GWAS) have identified several CRC susceptibility loci, including variants at 8q24 (near MYC), 11q23 (POU2AF1), 15q13 (GREM1), 18q21 (SMAD7), and 10p14, among others. Individually, these variants confer modest effect sizes, typically with odds ratios ranging from ~1.05 to 1.30; however, their combined burden, quantified as a Polygenic Risk Score (PRS), can substantially elevate lifetime CRC risk. However, most available PRS studies have been conducted in predominantly European populations, limiting generalizability across diverse ethnic groups. Prospective validation studies are required before routine clinical implementation can be recommended.

Notably, recent studies indicate that EO-CRC patients without a strong family history may exhibit a disproportionately high polygenic load, particularly in loci associated with insulin signalling, inflammation, and immune regulation. This supports a model in which polygenic susceptibility interacts with environmental exposures such as diet, obesity, and microbiome alterations to accelerate early carcinogenesis. Importantly, individuals in the highest PRS percentiles may reach a risk threshold comparable to that of carriers of moderate-penetrance germline mutations [32], suggesting potential utility for PRS-guided risk stratification and earlier screening initiation in younger populations. However, PRS has not yet been adequately validated in ethnically diverse EO-CRC cohorts, and prospective trials demonstrating clear clinical utility remain lacking. Additional challenges include population-specific calibration, variability in genetic architecture across ancestries, limited integration with environmental and lifestyle risk factors, and uncertainty regarding optimal clinical thresholds for screening implementation, together with cost-effectiveness considerations that have yet to be formally evaluated [29].

3. The Somatic Mutational Landscape

While germline mutations provide the background susceptibility for the disease, somatic mutations are the primary drivers of neoplastic progression [33]. Comparing the somatic landscape of sporadic EO-CRC, which is typically microsatellite stable (MSS),

against LO-CRC reveals subtle but biologically significant differences in driver gene frequencies and pathway activation.

3.1. Driver Gene Frequencies: A Distinct Hierarchy

Contrary to early hypotheses that EO-CRC would harbour a radically different set of driver genes, large scale sequencing studies from organizations such as Tempus, Foundation Medicine, and the TCGA have demonstrated that the overall mutational burden and the identity of driver genes are broadly similar to LO-CRC [34]. However, the frequency and clonality of these mutations differ, reflecting distinct selective pressures within the young colon [35].

3.1.1. TP53: The guardian breached early

Mutations in *TP53* are significantly more frequent in EO-CRC compared to LO-CRC, particularly in distal and rectal tumours [36]. In the classic Vogelstein adenoma carcinoma model of LO-CRC, *TP53* loss is a late event that mediates the transition from high grade adenoma to carcinoma [37]. Its high prevalence of approximately 70 to 77 % in EO-CRC suggests that young tumours may bypass early adenoma stages or progress through them rapidly. The increase in TP53 mutations is related to the elevated levels of chromosomal instability (CIN) and aneuploidy seen in these tumours [38]. TP53-mutated tumours may also exhibit increased sensitivity to DNA-damaging agents and PARP inhibitors through impaired DNA damage response signalling, although clinical data specifically in EO-CRC populations remain limited.

3.1.2. APC: The gatekeeper's variable role

The APC gene remains the most frequently mutated driver in both EO-CRC and LO-CRC; however, several large cohort analyses have reported modestly lower mutation frequencies in EO-CRC. For example, APC mutations have been reported in approximately 60–70% of EO-CRC cases compared to 75–85% in LO-CRC across datasets including TCGA and large commercial sequencing cohorts (e.g., Foundation Medicine, Tempus), although confidence intervals overlap across studies [39]. This relative reduction suggests that a subset of EO-CRC may arise through alternative Wnt pathway activation mechanisms, including CTNNB1 mutations or ligand-dependent signaling, rather than canonical APC loss [40]. At present, however, the observed differences in APC mutation frequency between EO-CRC and LO-CRC are primarily of biological and mechanistic significance rather than directly clinically actionable, as APC status currently has limited impact on routine therapeutic decision-making [41]. Should Wnt pathway inhibitors reach clinical maturity, APC mutation status may become more directly relevant for therapeutic selection in EO-CRC.

3.1.3. BRAF: The age-related divergence

One of the most striking differentiators between the two groups is the status of *BRAF*. The *BRAF* V600E mutation is a hallmark of right sided, hypermethylated (CIMP High), MSI-H tumours in elderly women [42]. In stark contrast, *BRAF* V600E mutations are significantly less common in sporadic EO-CRC [35, 36]. Mechanistically, the relative absence of *BRAF* V600E in younger patients confirms that sporadic EO-CRC does not typically arise through the sessile serrated lesion pathway that leads to MSI-H cancer in the elderly [36]. When *BRAF* mutations do occur in young patients, they are more likely to be atypical, non V600E Class II or III mutations [43]. These variants send out different signals, usually by dimerization, and they are not as sensitive to anti-EGFR therapies as the V600E variant [44].

3.1.4. KRAS and the MAPK pathway paradox

Some studies show that KRAS mutations happen less often in EO-CRC than in LO-CRC, while others show that the rates are similar [45, 46]. Transcriptomic analysis reveals a key finding: the MAPK/ERK signalling pathway is often paradoxically upregulated in KRAS wild type EO-CRC tumours [47]. This MAPK signature without mutation suggests that there are other ways to turn on the pathway, like overexpressing growth factor receptors like EGFR or HER2, or changing the epigenetics of negative regulators. This discovery has significant therapeutic ramifications, indicating that young patients may derive benefits from the inhibition of the MAPK pathway, such as through MEK/ERK inhibitors, even in the absence of conventional driver mutations [48].

3.1.5. Additional recurrent mutations: NRAS, PIK3CA, and FBXW7

Beyond canonical drivers, several additional mutations exhibit variable frequencies between EO-CRC and LO-CRC. NRAS mutations appear to occur at similar or slightly lower frequencies in EO-CRC compared to LO-CRC, although data remain inconsistent across cohorts. In contrast, PIK3CA mutations, which activate the PI3K/AKT pathway, have been reported in approximately 10–20% of CRC cases overall, with some studies suggesting modest enrichment in younger patients, potentially reflecting metabolic and insulin signaling influences [36].

FBXW7, a tumor suppressor involved in ubiquitin-mediated degradation of oncogenic proteins such as MYC and cyclin E, has also been implicated in EO-CRC, with mutation frequencies ranging from 10–15%. Loss of FBXW7 function may contribute to genomic instability and therapeutic resistance. While these alterations are not exclusive to EO-CRC, their integration into pathway-level analyses supports a model of convergent signaling dysregulation involving Wnt, MAPK, and PI3K axes in younger patients [49].

3.2. Tumour Mutational Burden (TMB)

Sporadic EO-CRC usually has a low tumour mutational burden (TMB Low), which is in line with its microsatellite stable (MSS) status. This is different from the TMB High phenotype of Lynch Syndrome or sporadic MSI-H LO-CRC. The low neoantigen burden associated with MSS EO-CRC contributes to a relatively immune-excluded or 'immune-cold' tumor microenvironment, which is generally associated with limited responsiveness to immune checkpoint inhibitor monotherapy. However, emerging evidence indicates that a subset of MSS tumors may exhibit sensitivity to combination immunotherapeutic strategies, including regimens incorporating VEGF inhibitors, MEK inhibitors, or other microenvironment-modulating agents, highlighting an evolving therapeutic landscape [50, 51]. The low TMB phenotype observed in most EO-CRC tumors has important translational implications because tumor mutational burden is closely associated with neoantigen generation and immune recognition [52]. Consequently, MSS/TMB-low EO-CRC tumors generally demonstrate reduced infiltration by cytotoxic T lymphocytes and limited responsiveness to immune checkpoint inhibitor monotherapy compared with MSI-H tumors. This represents a major therapeutic challenge, as the majority of younger patients fall within this immune-cold molecular category [53].

Current research efforts are therefore increasingly focused on combination therapeutic strategies designed to enhance tumor immunogenicity, including dual checkpoint blockade, VEGF inhibition, MEK/ERK pathway targeting, radiotherapy-induced immune priming, microbiome modulation, and stromal remodeling approaches. However, predictive biomarkers capable of identifying immunotherapy-responsive MSS EO-CRC subsets remain incompletely defined and require further prospective investigation. Representative examples of such combination strategies under early-phase clinical investigation in MSS colorectal cancer include regorafenib plus nivolumab and regorafenib plus avelumab, although EO-CRC-specific outcome data are not yet available.

4. Molecular Subtypes and Pathway Activation

The Consensus Molecular Subtypes (CMS) classification offers the most comprehensive transcriptomic framework for elucidating CRC heterogeneity. The distribution of these subtypes varies considerably by age, indicating unique underlying biology [54].

4.1. CMS Distribution in EO-CRC

Recent studies have connected EO-CRC to the CMS framework, showing that there are different common subtypes. CMS2, characterized by canonical Wnt-driven signatures, is the most common type in EO-CRC, making up about 75% of sporadic cases. This is much higher than the 40% found in LO-CRC. These tumours have a lot of somatic Copy Number Alterations (SCNAs), a lot of activation of Wnt and MYC downstream targets, and a lot of Chromosomal Instability (CIN). CMS2's dominance matches the fact that EO-CRC is more common in the distal and rectal areas and that TP53 mutations are very common. It suggests that the normal way that CRC develops is sped up in young people, possibly because of hormonal or metabolic factors like IGF 1 signalling that work with Wnt signalling [55, 56].

While CMS1 constitutes approximately 14% of LO-CRC cases, CMS2 accounts for ~35-40%, CMS3 for ~13%, and CMS4 for ~23%, reflecting a more heterogeneous transcriptomic distribution in older patients (Figure 1). In contrast, EO-CRC demonstrates marked enrichment of the CMS2 subtype, particularly in distal MSS tumours. CMS1 in EO-CRC is almost exclusively driven by Lynch Syndrome, whereas sporadic, non-Lynch CMS1 remains extremely rare in patients under 35, reinforcing the observation that immune-active, hypermutated tumours in young patients are frequently hereditary until proven otherwise [57]. CMS3, characterized by KRAS mutations and metabolic dysregulation, is present but less dominant than CMS2. However, the metabolic deregulation observed in Flavonifractor-associated EO-CRC may represent an emerging microbiome-associated metabolic phenotype that is not fully captured by the current CMS framework, highlighting a limitation of existing transcriptomic classifications [57]. Importantly, the CMS classification system is primarily derived from bulk tumor transcriptomic profiling and may therefore obscure significant intratumoral heterogeneity, stromal variability, and regional sampling differences. This limitation may be particularly relevant in EO-CRC, where marked molecular heterogeneity and variable tumor microenvironment composition could influence subtype assignment and biological interpretation [58]. Finally, CMS4 is associated with epithelial to mesenchymal transition (EMT), stromal infiltration, and TGF beta activation. While less frequent in early-stage disease, CMS4 signatures are enriched in metastatic EO-CRC and are associated with the aggressive fibrotic phenotype seen in signet ring cell carcinomas [59]. This intratumoral heterogeneity has been directly demonstrated using multiregional transcriptomic profiling, which shows that CMS calls frequently differ across sampling sites within the same tumour and can influence prognostic interpretation [60].

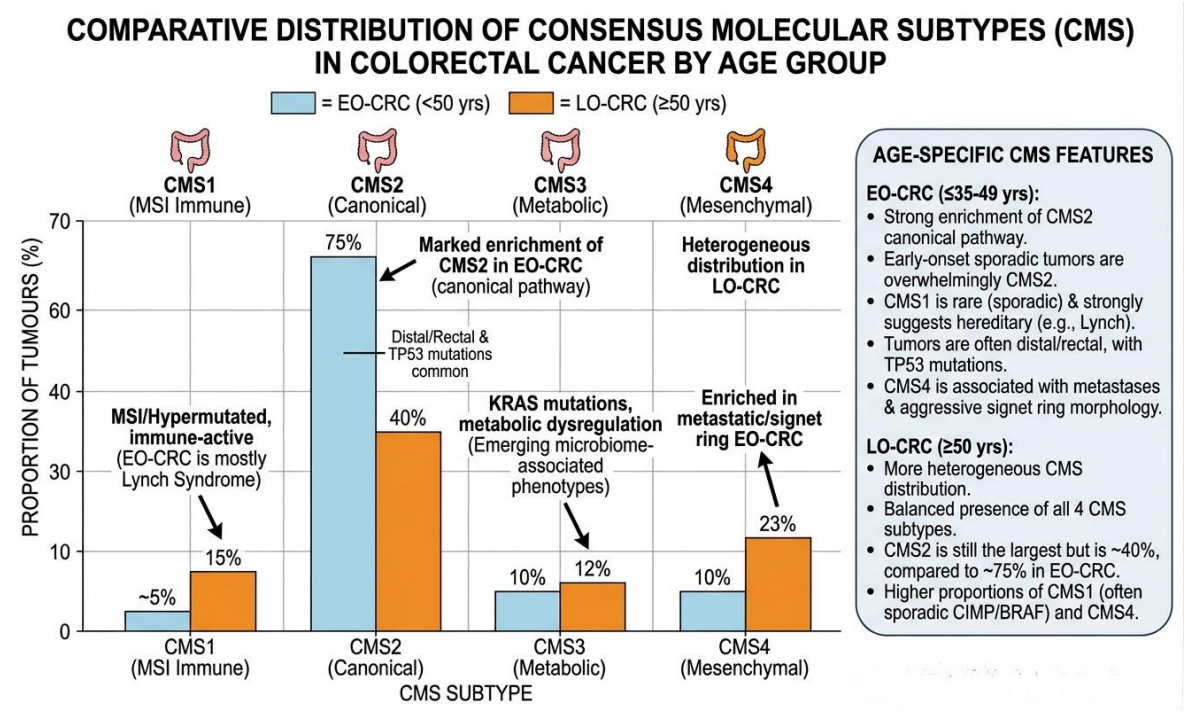


Figure 1. Comparative distribution of Consensus Molecular Subtypes (CMS) in EO-CRC and LO-CRC. EO-CRC demonstrates marked enrichment of the CMS2 canonical subtype, whereas LO-CRC exhibits a more heterogeneous distribution with higher proportions of CMS1 and CMS4 tumors.

4.2. Microsatellite and Chromosomal Instability

As previously noted, MSI-H in EO-CRC serves as a marker of germline defects associated with Lynch Syndrome. The sporadic MSI phenotype, which results from epigenetic *MLH1* silencing driven by aging and CpG island methylation, is a phenomenon of the elderly and is largely absent in the young [24].

The vast majority of sporadic EO-CRC is Microsatellite Stable (MSS) and exhibits high CIN. This genomic chaos typically manifests as extensive loss of heterozygosity (LOH), particularly at the 17p (*TP53*) and 18q (*SMAD4*) loci, and amplifications of oncogenes like *ERBB2* (HER2) and *MYC* [59]. The high CIN phenotype drives rapid evolution and drug resistance often observed in young patients. There is also a basic epigenetic difference when it comes to the CpG Island Methylator Phenotype (CIMP). LO-CRC is typically CIMP High, commonly linked to BRAF V600E and MLH1 methylation, whereas EO-CRC is mainly CIMP Low or CIMP Negative [61]. This substantiates that sporadic EO-CRC does not develop via the pronounced promoter hypermethylation pathway associated with aging. The vast majority of sporadic EO-CRC is Microsatellite Stable (MSS) and exhibits high chromosomal instability (CIN), whereas LO-CRC more frequently demonstrates MSI-H and CIMP-High phenotypes associated with aging-related MLH1 methylation and BRAF V600E mutations.

A comparative summary of the major molecular and epigenetic distinctions between EO-CRC and LO-CRC is presented in Table 2.

Table 2. Comparative Molecular and Epigenetic Features of EO-CRC and LO-CRC.

Feature	EO-CRC	LO-CRC
Microsatellite Status	Predominantly MSS	Mixed MSS/MSI-H
MSI-H Origin	Mainly Lynch syndrome	Mainly sporadic MLH1 methylation
CIMP Status	CIMP-Low / CIMP-Negative	Frequently CIMP-High
BRAF V600E	Rare	Common
Typical Location	Distal colon/rectum	Proximal colon
Dominant Pathway	CIN/Wnt-driven	Serrated/MSI pathway

Note: Table 2 presents qualitative categorical comparisons rather than evidence-graded findings. Criteria for evidence-strength grading (Strong/Moderate/Emerging), where used elsewhere in this review, are defined in the legends accompanying Table 3 and Table 8.

5. Epigenetic and Transcriptomic Dysregulation

While EO-CRC lacks the CIMP High phenotype, it is defined by a distinct and pervasive epigenetic landscape that appears heavily influenced by the exposome (Figure 2).

5.1. LINE-1 Hypomethylation: The Genome Unbound

One of the most powerful epigenetic markers in EO-CRC is the global hypomethylation of DNA, especially Long Interspersed Nuclear Element-1 (LINE 1). LINE 1 elements are retrotransposons, commonly referred to as jumping genes, constituting roughly 17% of the human genome [62]. In healthy somatic cells, these parts are heavily methylated and turned off to keep the genome stable. In EO-CRC, these elements frequently become hypomethylated, promoting transcriptional activation and retrotransposition, thereby contributing to genomic instability. This process can cause genomic instability by inserting into tumor suppressors or oncogenes, which can lead to double strand breaks and large-scale deletions [63]. There is some global hypomethylation in LO-CRC, but LINE 1 hypomethylation is much more severe in EO-CRC. This loss of methylation is associated with increased chromosomal instability, metastatic potential, and poorer prognosis in colorectal cancer. In EO-CRC, profound LINE-1 hypomethylation may reflect accelerated epigenomic aging driven by chronic inflammatory exposure, oxidative stress, metabolic dysfunction, and retrotransposon reactivation early in life. Consequently, although patients are chronologically younger, the tumor epigenome may appear molecularly ‘older’ or more destabilized than that observed in many LO-CRC tumors [64].

LINE-1 hypomethylation in EO-CRC is mechanistically linked to reduced activity of DNA methyltransferases (particularly DNMT1 and DNMT3B), as well as impaired maintenance methylation during rapid epithelial turnover. This loss of methylation permits transcriptional reactivation of retrotransposons, leading to increased reverse transcriptase activity, insertional mutagenesis, and accumulation of double-strand DNA breaks. In addition, LINE-1 activation can trigger cytosolic DNA sensing pathways such as cGAS-STING, promoting chronic innate immune activation and inflammatory signaling that further accelerates genomic instability [65]. Together, these processes establish a feedback loop between epigenetic erosion, immune activation, and chromosomal instability that may explain the accelerated "epigenetic aging" phenotype observed in EO-CRC tumors. However, EO-CRC-specific prognostic and therapeutic predictive data remain limited and require prospective validation.

From a therapeutic perspective, the reversible nature of epigenetic modifications raises the possibility that DNA methylation abnormalities may eventually become targetable. Although DNA methyltransferase inhibitors have demonstrated activity in certain hematological malignancies, their role in colorectal cancer remains investigational, and no epigenetic therapies are currently approved specifically for EO-CRC [66]. Future studies are needed to determine whether restoration of methylation homeostasis or modulation of epigenetic regulatory pathways can alter disease progression or treatment response in younger patients. Beyond LINE-1 and canyon-associated loci, genome-wide methylation profiling of ATP-binding cassette (ABC) transporter genes in CRC has revealed widespread hypomethylation relative to adjacent normal tissue, with numerous CpG sites demonstrating diagnostic value and prognostic correlation with patient survival, underscoring the broader contribution of methylation dysregulation to multidrug resistance in colorectal cancer [67]. While LINE-1 hypomethylation is reproducibly observed in EO-CRC, the causal role of specific environmental exposures and the contribution of this epigenetic alteration to tumour initiation versus tumour progression remain to be established. This concept of epigenetic age acceleration warrants further investigation as a potential biomarker of cumulative environmental exposure burden in EO-CRC. Whether the degree of LINE-1 hypomethylation correlates with specific clinical outcomes, such as metastatic potential or survival, has not yet been systematically characterized and represents an important direction for future study.

5.2. Methylation Canyon Erosion

Recent whole genome bisulfite sequencing (WGBS) has revealed methylation canyons, which are extensive genomic regions characterized by low methylation that encompass conserved developmental genes, including the HOX and PAX families. In EO-

CRC, hypermethylation causes the edges of these canyons to wear away. This erosion causes these important developmental regulators to not work properly, which could start embryonic growth programs again. This effect is stronger in EO-CRC than in LO-CRC, which suggests that there is a unique epigenetic mechanism for cancer growth [68, 69]. This could be because of certain environmental factors in early life, like toxins or dietary metabolites, that only affect chromatin modifiers. For readers less familiar with epigenetic regulation, PRC2 is a chromatin-modifying complex that silences gene expression through trimethylation of histone H3 at lysine 27 (H3K27me3), a repressive mark that helps maintain developmental genes in an inactive state.

Methylation canyon erosion is thought to arise from dysregulated balance between Polycomb repressive complex 2 (PRC2)-mediated histone modifications (H3K27me3) and DNA methylation machinery. In EO-CRC, disruption of this epigenetic crosstalk leads to progressive loss of boundary integrity at large regulatory domains controlling developmental transcription factors, including HOX clusters [70]. This erosion results in aberrant chromatin accessibility, inappropriate reactivation of embryonic gene expression programs, and destabilization of long-range enhancer promoter interactions. Such epigenomic reprogramming may contribute to lineage plasticity, tumor dedifferentiation, and increased stemness features characteristic of aggressive EO-CRC phenotypes [71].

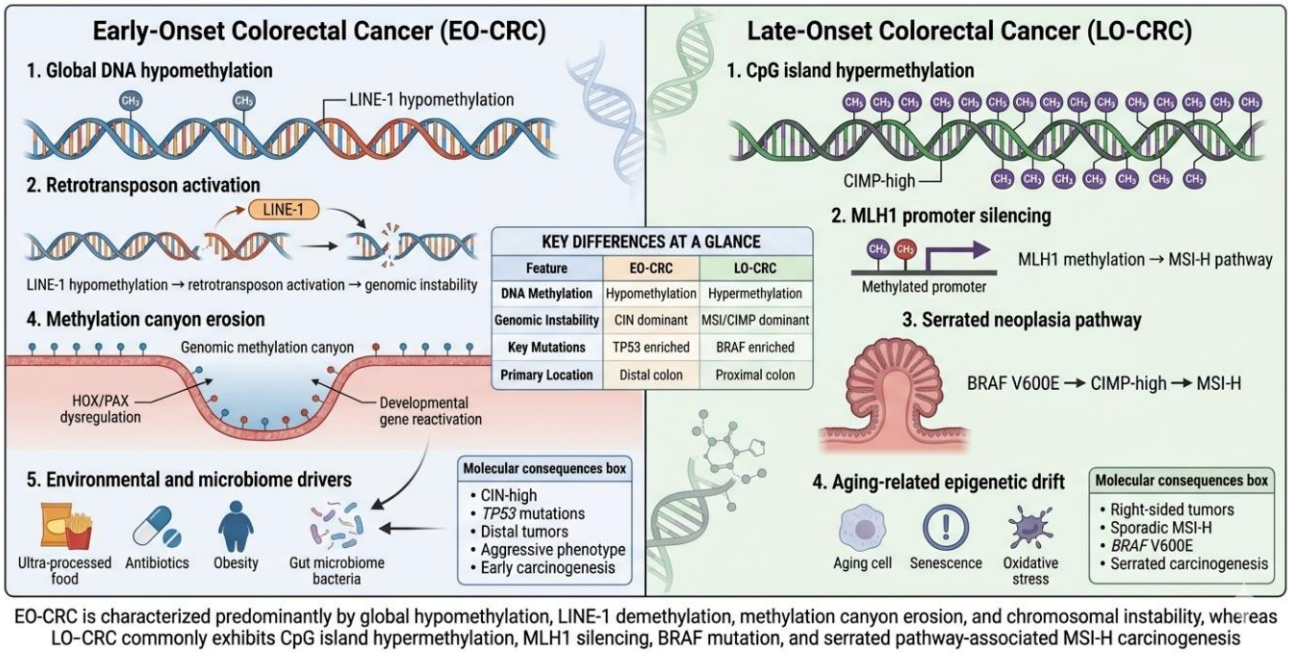


Figure 2. Comparative epigenetic landscapes of EO-CRC and LO-CRC.

5.3. Transcriptomic Signatures: Oxidative Stress and Splicing

Transcriptomic profiling, in addition to methylation, identifies functional enrichments that differentiate the younger cohort. EO-CRC tumours exhibit pronounced upregulation of NRF2-mediated oxidative stress response and glutathione metabolism genes [2]. This suggests that these tumours are developing in a microenvironment with high levels of reactive oxygen species (ROS), possibly caused by inflammatory diets or certain microbial metabolites.

Gene set enrichment analysis has also found that RNA splicing machinery is more active in EO-CRC. This results in unique alternative splicing events, exemplified by those in the lncRNA HOTAIRM1, which produce novel protein isoforms. These isoforms may exhibit oncogenic characteristics or function as neoantigens, further distinguishing the molecular biology of the disease in younger patients [72]. However, these transcriptomic observations are currently derived from relatively limited cohorts and require replication in larger, ethnically diverse multi-omics studies before definitive biological or therapeutic conclusions can be established.

6. The Microbiome and Metabolome: The Primary Link

Because 70 to 80% of EO-CRC cases are sporadic, the interaction between a diet characterized by westernized patterns, low fiber, and high processed meat consumption, the microbiome, and the host epithelium is regarded as the primary factor contributing to the increasing incidence [73]. Recent research has transitioned from basic association studies to the identification of specific causative microbial agents.

6.1. Flavonifractor plautii: A Specific Marker for the Young

Multi-omics studies integrating metagenomics and metabolomics have identified *Flavonifractor plautii* as a distinctive taxonomic marker of EO-CRC. This signal is largely absent or minimally detectable in LO-CRC and healthy controls [74]. *F. plautii* is a bacterium capable of metabolizing dietary flavonoids. Emerging metabolomic evidence suggests that *F. plautii* may contribute to carcinogenesis by metabolizing dietary flavonoids with known antioxidant and anti-inflammatory properties, potentially reducing their protective effects within the colonic microenvironment. However, this mechanism remains hypothetical and requires further experimental validation. This organism is linked to altered tryptophan metabolism, which may inhibit the host's immune response via aryl hydrocarbon receptor (AhR) signaling. This observation may support the future development of non-invasive stool-based screening strategies for younger populations. However, prospective validation in screening-eligible populations is required before clinical implementation, and the diagnostic

performance of *F. plautii* as an independent biomarker remains to be established [75]. Whether *F. plautii* abundance directly correlates with dietary flavonoid intake or specific dietary patterns in patients with EO-CRC has not yet been systematically examined and represents an important question for future dietary-microbiome studies.

6.2. pks+ Escherichia coli and the Colibactin Signature

The role of pks+ (polyketide synthase-positive) *Escherichia coli*, a bacterial species containing the pks genomic island that encodes the genotoxin colibactin, represents a significant mechanistic discovery in this domain. Colibactin induces DNA alkylation, resulting in double-strand DNA breaks, interstrand cross-links, and genomic instability. This specific damage causes Single Base Substitution signature 88 (SBS88), a unique mutational signature found in CRC genomes [76]. Clinically, colibactin-induced mutagenesis can be identified through mutational signature analysis, particularly Single Base Substitution signature 88 (SBS88), using whole-genome or whole-exome sequencing approaches. Detection of SBS88 in tumor samples may provide indirect evidence of prior exposure to pks+ *E. coli* and could eventually serve as a biomarker linking microbial genotoxicity to colorectal carcinogenesis [77].

Studies of organoids show that only colibactin-producing bacteria cause driver mutations in TP53 and APC. Importantly, these bacteria may exert their initial effects during childhood or adolescence. Colibactin may make it more likely that younger colonic epithelium will change. This is because it has a very active stem cell niche [74]. This fits with the hit-and-run theory, which says that bacteria can damage cells years before a person is diagnosed with cancer. Schematic illustration showing colonization by pks+ *Escherichia coli*, production of the genotoxin colibactin, induction of DNA alkylation and double-strand breaks, emergence of the SBS88 mutational signature, accumulation of TP53/APC driver mutations, chromosomal instability, and progression toward early-onset colorectal carcinogenesis (Figure 3).

The greater occurrence of pks+ *E. coli* in Western populations indicates a correlation among this microbial agent, geographical region, and dietary sources [78]. Experimental evidence from murine and intestinal organoid models further supports a causal role for colibactin-producing bacteria, as colonization with pks+ E. coli accelerates tumor formation and induces mutational profiles closely resembling those observed in human colorectal cancer [79]. Nevertheless, prospective longitudinal human studies establishing temporal causality remain limited. Whether antibiotic exposure during childhood or adolescence promotes colonization by pks+ *E. coli* has not been directly established and warrants dedicated investigation. Potential eradication strategies, including targeted probiotics,

bacteriophage therapy, and selective antimicrobial approaches, are being explored preclinically, although none has yet been validated in EO-CRC populations.

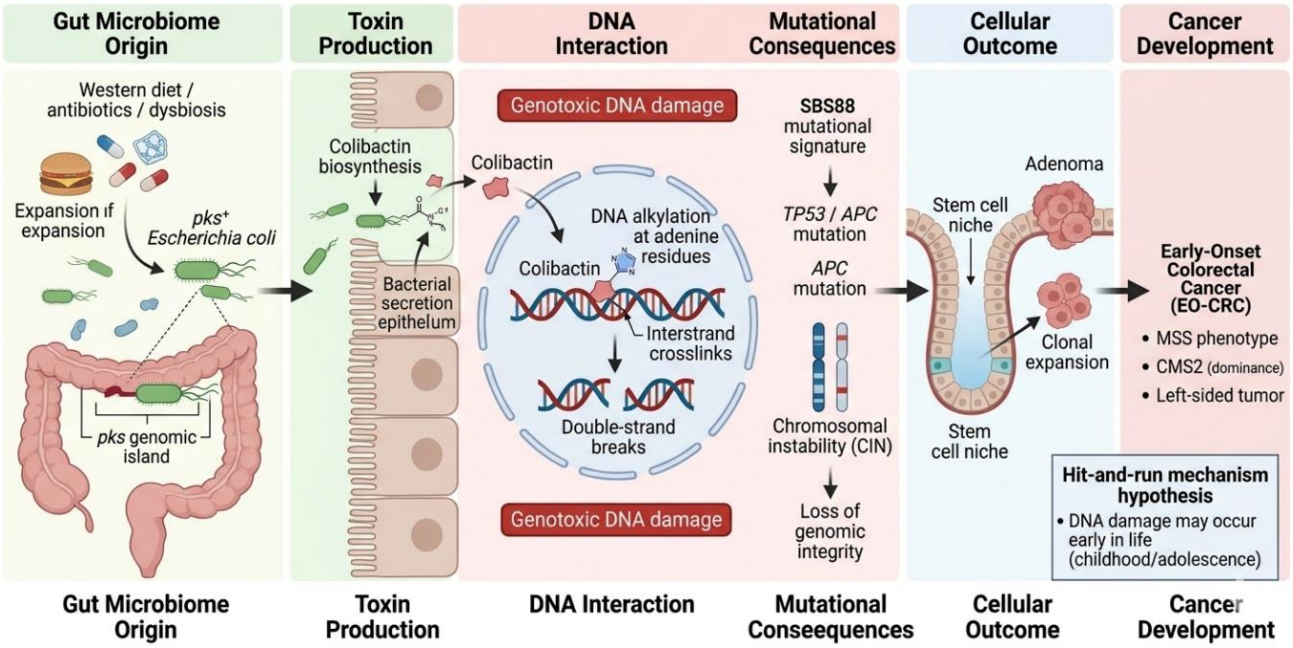


Figure 3. Mechanism of colibactin-mediated colorectal carcinogenesis in EO-CRC. Schematic illustration showing colonization by pks+ *Escherichia coli*, production of the genotoxin colibactin, induction of DNA alkylation and double-strand breaks, emergence of the SBS88 mutational signature, accumulation of TP53/APC driver mutations, chromosomal instability, and progression toward early-onset colorectal carcinogenesis.

6.3. Fusobacterium nucleatum: A Point of Divergence

Fusobacterium nucleatum, a well-known pathogen in colorectal cancer (CRC), adheres to E-cadherin and suppresses the activation of natural killer (NK) cells. However, evidence suggests that although F. nucleatum can also be detected in EO-CRC cohorts, it appears less age-specific than F. plautii and remains more consistently associated with MSI-H, CIMP-high, and right-sided tumours typically observed in LO-CRC, particularly MSI-H and CIMP High tumours [80]. The *F. plautii* versus *F. nucleatum* dichotomy may indicate a shift in microbial ecology, although some studies continue to identify it in EO-CRC. In young individuals, dysbiosis appears to be induced by specific metabolic strains, whereas in older adults, it may result from intestinal barrier failure and oral-gastrointestinal translocation [81]. Importantly, microbial associations appear to vary across geographic regions and ethnic populations, likely reflecting differences in dietary habits, antibiotic exposure, host genetics, and environmental factors. Several Western cohorts report stronger enrichment of pks+ E.

coli, whereas Asian studies have identified broader microbial heterogeneity, underscoring the need for population-specific microbiome validation studies [82].

6.4. Metabolomic Shifts: Bile Acids and Choline

Metabolomic profiling of EO-CRC patients indicates considerable dysregulation in bile acid and choline metabolism. High-fat diets increase the production of primary bile acids, which are subsequently converted by gut microbiota. Gut bacteria then change these into secondary bile acids like deoxycholic acid. These secondary bile acids are strong carcinogens that can damage DNA and cause long-term inflammation. The microbiome of young patients, possibly modified by antibiotics or early life nutrition, seems more adept at this toxic transformation. This makes the distal colon a place where these metabolites build up and can cause cancer [83, 84]. Additional metabolomic alterations have also been implicated in EO-CRC, including reduced production of protective short-chain fatty acids (SCFAs), particularly butyrate, and altered trimethylamine-N-oxide (TMAO) metabolism. Reduced butyrate levels may impair epithelial barrier integrity and anti-inflammatory signaling, while elevated TMAO has been associated with chronic inflammation, oxidative stress, and carcinogenic metabolic environments [85]. A comparative overview of key microbial and metabolomic alterations identified in EO-CRC and LO-CRC is summarized in Table 3. These metabolomic shifts are hypothesized to be driven in part by Westernized, high-fat dietary patterns, although direct evidence linking specific dietary exposures to these metabolomic alterations in EO-CRC cohorts remains limited.

From a translational perspective, these microbial signatures may provide opportunities for non-invasive early detection strategies in younger populations who fall outside conventional screening age thresholds. In particular, stool-based detection of *Flavonifractor plautii* DNA, either alone or in combination with microbial and methylation biomarkers, has been proposed as a potential screening approach for EO-CRC. Likewise, identification of colibactin-associated mutational signatures such as SBS88 in stool-derived DNA or circulating tumour DNA may help identify individuals exposed to genotoxic pks+ *Escherichia coli* [86–88]. Although these approaches remain investigational, they highlight the potential integration of microbiome-informed diagnostics into future age-stratified screening programs. Collectively, these findings support a multi-step model in which environmental exposures interact with microbial dysbiosis, genotoxic injury, and host molecular alterations to promote the development of CMS2-dominant EO-CRC (Figure 4).

Table 3. Comparative Microbial and Metabolomic Signatures in EO-CRC and LO-CRC.

Microbial/Metabolic Feature	EO-CRC	LO-CRC	Proposed Mechanism	Evidence* Strength
Flavonifractor plautii	Enriched	Rare/minimal	Flavonoid depletion, immune modulation	Emerging
pks+ *E. coli*	Frequently enriched	Variable	Colibactin-mediated DNA damage (SBS88)	Strong
Fusobacterium nucleatum	Present in subsets	Common	Immune evasion, inflammation	Strong
Secondary bile acids	Increased	Increased	DNA damage, inflammation	Moderate
Butyrate (SCFAs)	Reduced	Variable	Loss of epithelial protection	Emerging
TMAO metabolism	Altered	Less defined	Oxidative stress, inflammation	Emerging

*Evidence strength was categorized as: Strong: replicated in three or more independent cohorts and supported by mechanistic or experimental evidence, Moderate: supported by two independent cohorts or a single cohort with complementary experimental validation, Emerging: based primarily on single-cohort studies, preliminary datasets, or findings requiring independent replication.

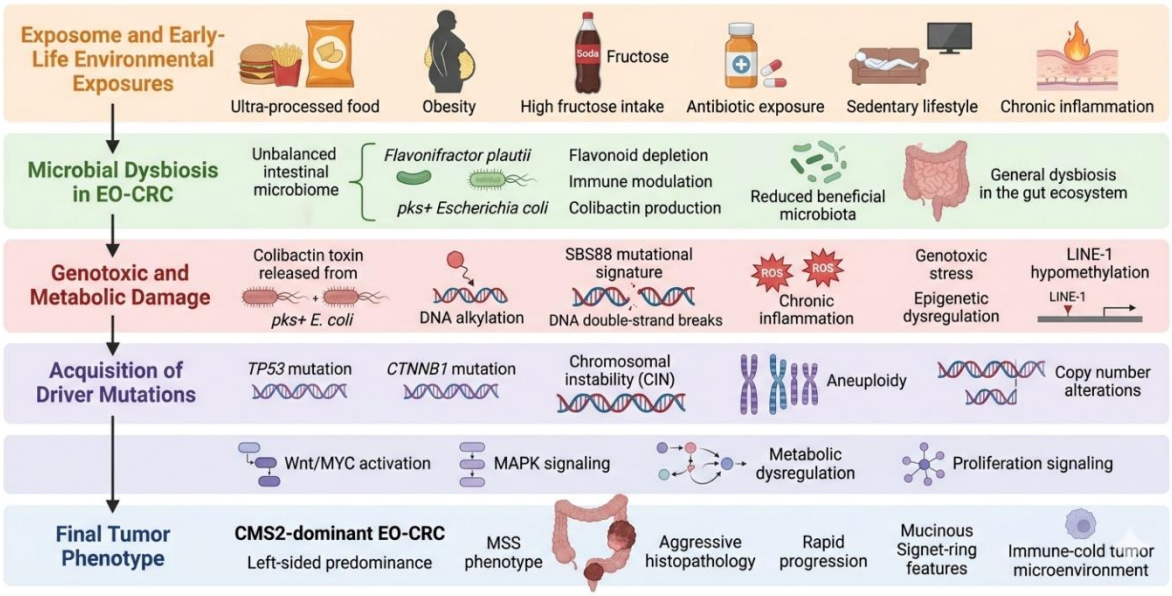


Figure 4. Proposed multi-step pathogenesis model of early-onset colorectal cancer (EO-CRC). Schematic illustration showing how exposome-related factors, including Westernized diet, obesity, antibiotic exposure, and metabolic dysfunction, contribute to microbial dysbiosis characterized by enrichment of *Flavonifractor plautii* and pks+ *Escherichia coli*. Colibactin-mediated DNA damage induces SBS88 mutational signatures and promotes acquisition of driver mutations such as TP53 and CTNNB1 alterations, chromosomal instability, epigenetic dysregulation, and activation of Wnt/MYC signalling pathways, ultimately contributing to the development of CMS2-dominant EO-CRC.

6.5. Methodological Challenges in Microbiome Research

Interpretation of microbiome associations in EO-CRC remains complicated by substantial methodological heterogeneity across studies. Many early investigations relied on 16S rRNA sequencing, which provides limited taxonomic resolution and restricted functional characterization compared with whole-genome shotgun metagenomics [89]. Differences in stool versus mucosal sampling, DNA extraction protocols, sequencing platforms, bioinformatic pipelines, dietary confounders, and antibiotic exposure history may also contribute to inter-study variability and inconsistent microbial signatures [90]. In addition, batch effects and small cohort sizes remain major limitations in current EO-CRC microbiome studies, particularly given the relatively low incidence of disease in younger populations [91]. Future large-scale prospective studies integrating standardized sampling methods with metagenomic, metabolomic, and host transcriptomic profiling will be essential to improve reproducibility and clarify causal microbial mechanisms. A concise summary of the most robust microbiome-associated findings and major unresolved questions in EO-CRC is presented in Table 4.

Table 4. Microbiome Summary Box: Key Findings and Outstanding Questions in EO-CRC.

Most Robust Findings	**Major Unresolved Questions**
Enrichment of pks+ Escherichia coli in EO-CRC Multiple studies have identified increased prevalence of colibactin-producing pks+ *E. coli* in EO-CRC. Experimental evidence supports a direct genotoxic role through induction of DNA damage and SBS88 mutational signatures.	**Driver versus Passenger Debate** Do microbial alterations actively initiate tumorigenesis, or do they preferentially colonize established tumours?
Distinct Microbial and Metabolomic Profiles in EO-CRC Emerging multi-omics studies suggest EO-CRC exhibits microbial communities and metabolomic signatures that differ from those observed in LO-CRC, including enrichment of *Flavonifractor plautii* and altered bile acid metabolism.	**Temporal Relationship** At what stage of life do microbial exposures contribute to carcinogenesis, and how long before diagnosis do these effects occur?
Interaction Between Microbiome, Host Genetics, and the Exposome Current evidence supports a model in which environmental exposures, microbial dysbiosis, and host molecular susceptibility collectively contribute to EO-CRC pathogenesis.	**Clinical Utility** Can microbial biomarkers reliably improve risk prediction, early detection, or therapeutic stratification in prospective screening populations?

Abbreviations: EO-CRC, early-onset colorectal cancer; SBS88, single base substitution signature 88.

6.6. Microbiome Causality and Interpretation

Despite growing evidence linking microbial dysbiosis to EO-CRC, important questions remain regarding causality and biological interpretation of these associations. While the associations with *Flavonifractor plautii* and pks+ *Escherichia coli* are statistically robust, longitudinal data proving causality in humans are still lacking. A major unresolved issue in EO-CRC microbiome research is the "driver-versus-passenger" debate, namely whether these microbial species actively initiate carcinogenesis or preferentially colonize an already established tumour microenvironment. Distinguishing between these possibilities is essential for determining whether microbial-targeted interventions may be effective for prevention or early detection.

Current evidence most strongly supports a potential driver role for colibactin-producing pks+ *Escherichia coli*. Mechanistic studies have demonstrated that colibactin induces DNA alkylation, double-strand DNA breaks, chromosomal instability, and the characteristic SBS88 mutational signature observed in colorectal cancer genomes. Experimental evidence from murine models and intestinal organoid systems further shows that exposure to pks+ *E. coli* can induce oncogenic mutations in driver genes such as TP53 and APC, supporting a direct carcinogenic role. The "hit-and-run" hypothesis additionally proposes that transient microbial exposure during childhood or adolescence may initiate mutagenic events years before clinical tumor detection [78].

In contrast, the pathogenic role of *Flavonifractor plautii* remains less definitively established. Although metagenomic and metabolomic studies consistently demonstrate enrichment of *F. plautii* in EO-CRC, current evidence remains largely associative. Proposed mechanisms include flavonoid depletion, altered tryptophan metabolism, and immune modulation through aryl hydrocarbon receptor (AhR) signaling; however, direct experimental validation remains limited. It is therefore possible that *F. plautii* may function as a tumour-associated passenger organism rather than a primary carcinogenic driver [75].

Importantly, established colorectal tumours create hypoxic, inflammatory, and metabolically altered microenvironments that may selectively favor colonization by specific microbial communities. Tumour-associated mucus disruption, immune dysregulation, altered nutrient availability, and epithelial barrier dysfunction may further contribute to secondary microbial enrichment. Consequently, microbial enrichment alone should not be interpreted as definitive evidence of causality [92]. Beyond its mechanistic role in carcinogenesis, the microbiome may also offer novel opportunities for early detection, risk stratification,

prevention, and therapeutic intervention. A summary of potential clinical applications and current evidence is presented in Table 5.

Table 5. Clinical Microbiome Applications in Early-Onset Colorectal Cancer (EO-CRC).

Application Area	Current Evidence	Clinical Potential	Major Limitations
Stool-Based Microbial DNA Detection	Detection of microbial signatures such as *Flavonifractor plautii*, *pks+ Escherichia coli*, and microbial gene markers has shown promise in observational studies.	May complement existing stool-based screening approaches and help identify younger individuals who fall below current screening age thresholds.	Prospective validation in screening populations is lacking; diagnostic sensitivity and specificity remain uncertain.
Microbiome-Informed Risk Stratification	Integration of microbial profiles with genetic, epigenetic, and metabolomic biomarkers is being explored.	Could support personalized risk prediction models and earlier screening strategies.	No validated EO-CRC-specific risk models currently exist.
Probiotic and Prebiotic Interventions	Experimental studies suggest modulation of gut microbial composition may reduce inflammation and restore production of beneficial metabolites such as butyrate.	Potential preventive strategy through enhancement of epithelial barrier function and reduction of carcinogenic microbial activity.	Evidence remains largely preclinical; optimal microbial strains, dosage, and long-term efficacy are unknown, and no randomized controlled trials have been conducted specifically in EO-CRC populations.
Dietary Microbiome Modulation	High-fiber diets may increase short-chain fatty acid production and reduce bile acid-associated carcinogenesis.	Represents a scalable population-level prevention strategy.	Direct evidence in EO-CRC prevention remains limited.
Fecal Microbiota Transplantation (FMT)	FMT has demonstrated efficacy in selected gastrointestinal disorders and is under investigation for cancer-related microbiome modulation.	May eventually be used to restore healthy microbial ecosystems or improve treatment responsiveness.	No clinical studies have specifically evaluated FMT in EO-CRC, and this absence of dedicated evidence should be regarded as a major limitation; safety, durability, and patient selection remain unresolved.
Microbiome-Targeted Therapeutics	Strategies targeting colibactin-producing *pks+ Escherichia coli* and microbial metabolic pathways are under development.	Potential for precision prevention and adjunctive therapy.	Currently investigational and supported primarily by mechanistic and preclinical studies.

Future research priorities for translating these microbiome findings into clinical practice include prospective, adequately powered validation studies of stool-based microbial biomarkers in screening-eligible populations; randomized controlled trials of probiotic, prebiotic, and microbiome-targeted interventions specifically enrolling patients with EO-CRC; and standardized protocols for sample collection and bioinformatic analysis to enable cross-study comparison. Achieving these goals will be essential for translating microbiome-informed risk stratification and prevention strategies into routine clinical implementation.

7. Clinical-Pathological Correlation and the Age Cutoff Debate

Different clinical and pathological characteristics are indicative of the unusual genetic architecture of early onset colorectal cancer (EO-CRC). Accurate risk assessment and management for clinicians depends on their comprehension of these relationships.

7.1. Anatomical Sidedness: The Left Side Shift

EO-CRC predominantly affects the left side, particularly the distal colon and rectum, while late onset colorectal cancer (LO-CRC) exhibits a more uniform distribution or is restricted to the right side. The anatomical distribution also reflects important molecular and microenvironmental differences between proximal and distal colorectal tumors. While embryological origin contributes to these distinctions, accumulating evidence suggests that differences in molecular pathways, microbiome composition, immune signaling, and epigenetic regulation may play a more direct role in shaping the left-sided predominance observed in EO-CRC [93]. The frequency of TP53 mutations and CMS2 subtypes in early-onset colorectal cancer corresponds precisely with the established biology of distant tumours. Conversely, right-sided LO-CRC is generally associated with BRAF mutations and MSI-H characteristics indicative of midgut origins. From a clinical standpoint, this distal position determines the symptomatology, frequently characterized by rectal haemorrhage, alterations in bowel habits, and tenesmus. A distinctive diagnostic delay often arises because these symptoms are frequently ignored as benign illnesses such as haemorrhoids or fissures in young, healthy persons [94]. Beyond its diagnostic and biological significance, anatomical sidedness also carries therapeutic relevance: left-sided tumours are generally more responsive to anti-EGFR therapies such as cetuximab and panitumumab than right-sided tumours, a consideration directly applicable given the predominantly left-sided distribution of EO-CRC.

7.2. Histopathological Aggression

Histologically, EO-CRC tumors tend to exhibit greater aggressiveness compared to LO-CRC tumors. They are much more likely to be poorly differentiated and have a lot more

mucinous and signet ring cell histology than normal [76, 95]. Signet ring cell carcinoma is uncommon in LO-CRC, representing approximately 1% of all colorectal cancers overall; however, studies of very early-onset disease report frequencies ranging from 5–13% in patients under 35 years of age, highlighting its disproportionate enrichment in younger cohorts [96]. The molecular basis for the signet ring shape is often associated with the reduced expression of E-cadherin (CDH1) and a marked mesenchymal or stem-like condition similar to the CMS-4 subtype. This molecular profile is associated with the tumour's aggressive and invasive characteristics, their propensity to metastasize to the peritoneum or to manifest as carcinomatosis, as well as their inherent resistance to conventional chemotherapy regimens [97].

7.3. The Age Cutoff Debate: Under 35 vs. 40 to 50

Recent literature has begun to challenge the exclusive definition of under 50 for this disease, suggesting that patients under 35 represent a unique biological subgroup when compared to those aged 40 to 50 [98, 99]. Individuals classified within the very early onset category, particularly those under the age of 35, exhibit the highest occurrence of signet ring cells and the most significant prevalence of genetic predispositions, even if these conditions remain unacknowledged at present. Their sporadic cases often show a reduced mutational burden, which many researchers consider to be the true EO-CRC phenotype. Conversely, the 40 to 50 age demographic resembles LO-CRC in its clinical presentation, despite being the group responsible for the increasing incidence. Tumours within this intermediate category are likely the result of the cumulative exposome, which encompasses factors such as obesity and metabolic syndrome, interacting with a typical colorectal cancer pathway. This group effectively bridges the biological divide between diseases that manifest in early life and those that emerge later [100].

These observations have important clinical implications. Patients under 35 years of age may require a distinct diagnostic and management framework due to their higher prevalence of hereditary syndromes, aggressive histopathology, and advanced-stage presentation [101]. Although population-wide screening below age 45 is currently not considered cost-effective, several experts have proposed risk-adapted approaches incorporating family history, polygenic risk scores, inherited cancer syndromes, and early warning symptoms to identify high-risk younger individuals for earlier colonoscopy evaluation [102]. Current evidence supports a risk-adapted screening framework rather than universal screening in younger adults. Individuals with a strong family history of CRC, known hereditary cancer syndromes, elevated polygenic risk scores, persistent rectal bleeding, unexplained iron deficiency anemia, or multiple risk factors such as obesity and

inflammatory bowel disease may warrant earlier colonoscopy evaluation before the standard screening age [103]. In addition, clinicians may need a lower threshold for diagnostic colonoscopy in symptomatic adults under 35 presenting with persistent rectal bleeding, unexplained iron deficiency anemia, or altered bowel habits [104]. However, survival data remain conflicting across studies. Some cohorts report improved overall survival among younger patients due to greater physiological resilience and ability to tolerate intensive multimodal therapy, whereas others demonstrate poorer stage-adjusted outcomes, particularly among patients under 35 years of age who present with advanced disease, aggressive histopathological features, and delayed diagnosis. These findings suggest that chronological age alone may be an insufficient predictor of prognosis in EO-CRC [105]. A practical summary of clinical features that should prompt consideration of EO-CRC in adults younger than 35 years is provided in Table 6. This summary is intended primarily to raise clinical suspicion and support referral decisions in practice, rather than to serve as a validated research stratification instrument.

Collectively, these findings also have led some investigators to propose a two-tier classification framework consisting of very early-onset CRC (<35 years) and early-onset CRC (35–49 years). Under this model, patients younger than 35 years appear more strongly enriched for hereditary predisposition, signet ring histology, and aggressive disease biology, whereas patients aged 35–49 years more closely resemble the molecular and clinical characteristics of conventional CRC influenced by cumulative environmental and metabolic exposures [98]. Although this classification has not yet been universally adopted, it may provide a more biologically meaningful framework for future research and risk stratification. The clinical utility of this classification requires prospective validation, but it may help guide risk stratification, genetic testing prioritization, and clinical trial enrollment strategies.

Table 6. When to Suspect Early-Onset Colorectal Cancer (EO-CRC) in Patients Under 35 Years of Age.

Category	Clinical Features Suggesting EO-CRC
High-Risk Symptoms	• Persistent rectal bleeding • Unexplained iron deficiency anaemia • Change in bowel habits lasting >4–6 weeks • Persistent abdominal pain • Unintentional weight loss • Tenesmus
Family History and Genetic Risk	• First-degree relative with colorectal cancer • Family history suggestive of Lynch syndrome • Known hereditary cancer syndrome • Multiple affected relatives across generations

Clinical Features Increasing Suspicion	• Left-sided colorectal symptoms without an alternative diagnosis • Recurrent symptoms despite treatment for presumed benign conditions (e.g., haemorrhoids) • Combination of rectal bleeding and altered bowel habits • Early-onset adenomatous polyps
Suggested Clinical Action	• Lower threshold for referral to diagnostic colonoscopy • Consider genetic counselling and germline testing when hereditary risk factors are present

8. Comparative Summary Table

Table 7 combines the key molecular and clinical distinctions identified in this review.

Table 7. A Comparison of Early-Onset and Late-Onset Colorectal Cancer.

Feature	Early-Onset CRC (EO-CRC)	Late-Onset CRC (LO-CRC)	Clinical Implications
Age Definition	Typically, <50 years (Distinct subset <35)	≥50 years	Supports lowering routine screening initiation age and distinct diagnostic protocols for patients under 35
Anatomical Distribution	Distal Colon & Rectum (>70%) [12]	Proximal (Right) & Distributed [61]	Favors flexible sigmoidoscopy or rectal examination as adjuncts where colonoscopy access is limited
Germline Predisposition	High (~16-25%); Lynch Syndrome dominant [106]	Low (~5%); Sporadic [106]	Reinforces universal germline multigene panel testing for all patients diagnosed before age 50
Heritability Type	High "Missing Heritability" / Polygenic Risk	Low; sporadic somatic aging	Highlights the need for polygenic risk score development and validation in younger cohorts
Key Driver Mutations	TP53, CTNNB1 (High frequency) [35]	APC, KRAS, BRAF (High frequency)	May inform future eligibility for TP53- and Wnt-pathway-directed therapeutic trials
BRAF Status	V600E Rare (<5%); non-V600E more common [107]	V600E Common (~15–20%) [107]	Non-V600E variants require confirmation before excluding anti-EGFR therapy eligibility
Microsatellite Status	MSI-H in ~15-20% (Mostly Lynch) [12]	MSI-H in ~15% (Sporadic MLH1 methyl.)	MSI-H status in EO-CRC should prompt Lynch syndrome workup rather than an assumption of sporadic origin
CIMP Status	CIMP-Low / Negative [61]	CIMP-High (CpG Island Methylator)	Limits the utility of CIMP-based risk models developed in older populations
CMS Subtype	CMS2 (Canonical) Dominant (~75%) [57]	Mixed; CMS1 (Immune), CMS3 (Metabolic)	Supports prioritization of Wnt-pathway-directed and MEK/ERK-targeted trial enrollment
Epigenetic Signature	LINE-1 Hypomethylation; Canyon Erosion	Genome-wide Hypermethylation (Aging)	Raises the possibility of epigenetic biomarkers for risk stratification, pending validation
Microbiome	*Flavonifractor plautii*, *pks+ E. coli*	*Fusobacterium nucleatum*, *B. fragilis*	Supports development of stool-based microbial biomarkers for non-invasive early detection
Histopathology	Mucinous, Signet-Ring, Poorly Diff. [95]	Adenocarcinoma NOS (Glandular)	Aggressive histology warrants close surveillance and more intensive staging workup
Stage at Diagnosis	Advanced (III/IV); Diagnostic Delay [95]	Early (I/II) via screening	Reinforces the need to reduce diagnostic delay and lower the threshold for colonoscopy referral

MSI-H Tumor's and Immunotherapy	Lynch-associated MSI-H tumors generally demonstrate favorable responses to immune checkpoint inhibitors	Sporadic MSI-H/CMS1 tumors commonly respond to immune checkpoint inhibitors	Supports first-line immune checkpoint inhibitor use in confirmed Lynch-associated MSI-H disease
MSS Tumor's and Immunotherapy	Majority of MSS/CMS2 tumors are immune-cold and demonstrate limited response to checkpoint inhibitor monotherapy; combination immunotherapy approaches are under investigation	MSS tumors similarly show limited response to checkpoint inhibitor monotherapy, with ongoing evaluation of combination strategies	Favors enrollment in combination immunotherapy trials rather than checkpoint monotherapy
Recommended Germline Testing	Universal multigene panel testing recommended for all patients diagnosed before age 50	Testing guided by family history, tumor characteristics, and clinical criteria, although broader testing is increasingly considered	Universal testing should be incorporated into standard diagnostic workup at initial presentation

Abbreviations: MSI-H, microsatellite instability-high; MSS, microsatellite stable; CIN, chromosomal instability; CMS, Consensus Molecular Subtype; CIMP, CpG Island Methylator Phenotype.

Note: Percentages and frequencies shown are approximate ranges synthesized from multiple cohort studies and large genomic datasets and may vary across populations and study designs.

9. Gap Analysis: Missing Links and Controversies

Notwithstanding substantial progress in comprehending early onset colorectal cancer (EO-CRC), some fundamental deficiencies persist, posing continual challenges for both researchers and physicians.

9.1. The Sporadic Black Box

Approximately 20% of cases have been associated with germline factors. The remaining 80% are presently referred to as sporadic; however, their distinct molecular characteristics, such as the enrichment of *Flavonifractor plautii* and hypomethylation of LINE 1, suggest a particular underlying cause that transcends mere randomness. The exact environmental triggers, whether they are certain dietary additives like emulsifiers, a certain type of antibiotic, or the buildup of microplastics, are still unknown. Identifying these particular exposures is crucial for developing effective primary prevention strategies [108].

9.2. Missing Heritability

The role of deep intronic variants, epigenetic heritability involving imprinting defects that are not captured by standard sequencing, and the implementation of validated Polygenic Risk Scores in diverse populations represent the next research frontier. There is a clear need to move beyond monogenic models to understand how cumulative genetic risk contributes to early oncogenesis [109].

9.3. Sex-Specific Differences

Another underexplored area in EO-CRC research is the role of sex-specific biological differences. Several epidemiological studies have reported differing incidence trends and

anatomical distributions between male and female patients with EO-CRC, with some cohorts showing a disproportionately rising burden among younger women, particularly for rectal cancer [110]. Hormonal influences, adiposity patterns, immune responses, microbiome composition, and dietary exposures may contribute to these observed differences; however, the molecular basis remains poorly defined [111]. Furthermore, sex-specific variation in immune signaling, bile acid metabolism, and microbiome-host interactions may influence tumor biology and therapeutic response [112]. Future studies integrating sex-stratified genomic, transcriptomic, and microbiome analyses are necessary to determine whether EO-CRC should incorporate sex-informed risk stratification and treatment approaches.

9.4. Immunotherapy Resistance

Despite increasing understanding of the molecular and immune landscape of EO-CRC, major knowledge gaps remain regarding mechanisms of immunotherapy resistance in MSS/CMS2 tumors, which constitute the majority of EO-CRC cases [113]. Most current therapeutic approaches have been extrapolated from studies of average-onset CRC, and EO-CRC-specific prospective data remain limited [114]. Future research should focus on identifying predictive biomarkers of immunotherapy response, defining age-specific tumor microenvironment characteristics, and developing therapeutic strategies capable of overcoming immune exclusion in MSS EO-CRC. A major unresolved question is whether the immune-cold phenotype of MSS EO-CRC reflects intrinsic tumour biology, early-life immune programming, or microbiome-mediated immunosuppression; elucidating these mechanisms will be essential for developing rational combination immunotherapeutic strategies.

9.5. Microbiome Causality

A major limitation of current EO-CRC microbiome studies is that most remain cross-sectional and cannot establish temporal relationships between dysbiosis and tumour initiation. Resolving the driver-versus-passenger debate will therefore require longitudinal prospective cohort studies utilizing pre-diagnostic stool samples, alongside mechanistic investigations using germ-free animal models, fecal microbiota transplantation (FMT), organoid co-culture systems, and CRISPR-based microbial functional studies. Integration of metagenomics with host transcriptomic, epigenomic, and metabolomic profiling may further clarify whether microbial dysbiosis actively contributes to EO-CRC pathogenesis or primarily reflects tumour-associated ecological remodelling [78].

9.6. Lack of Faithful Preclinical Models

A major barrier to mechanistic and translational EO-CRC research is the lack of preclinical models that accurately recapitulate the biological features of the disease. Most currently available colorectal cancer organoids, patient-derived xenografts, and genetically engineered mouse models have been developed from average-onset CRC and may not adequately capture the unique molecular, epigenetic, microbial, and exposome-associated characteristics of EO-CRC [115]. In particular, existing models rarely incorporate age-specific microbiome interactions, early-life environmental exposures, or the CMS2-dominant molecular phenotype frequently observed in younger patients [116]. The development of EO-CRC-specific organoid platforms, microbiome-integrated experimental systems, and age-relevant animal models will be essential for validating causal mechanisms and accelerating therapeutic discovery.

9.7. Lack of Prospective Longitudinal Studies with Pre-Diagnostic Biospecimens

Most current EO-CRC molecular and microbiome studies are cross-sectional or rely on biospecimens collected at the time of diagnosis, precluding assessment of temporal relationships between putative risk exposures and tumour initiation. Prospective cohorts incorporating pre-diagnostic stool, blood, or tissue biospecimens will be essential to clarify whether the molecular and microbial features associated with EO-CRC precede tumorigenesis or instead reflect tumour-associated ecological remodelling.

10. Future Directions and Precision Medicine

The distinct biology of early onset colorectal cancer (EO-CRC) necessitates a fundamental recalibration of both clinical management and public health strategy.

10.1. Age Specific Screening and Risk Stratification

The recent decision by the USPSTF and NCCN to lower the universal screening age to 45 only helps people between the ages of 45 and 49. It doesn't help people under 35, who often have the most aggressive disease. Age should not be the only factor in future screening plans. Combining Polygenic Risk Scores (PRS) with detailed family history, lifestyle exposures, and inherited cancer syndromes into integrated risk prediction models may help identify young adults who could benefit from earlier screening initiation, potentially beginning between ages 30 and 35 [117]. Future screening strategies will likely move beyond age alone and incorporate individualized risk assessment. Integrated models combining family history, hereditary cancer syndromes, lifestyle exposures, and validated genetic risk markers may help identify younger individuals who would benefit from earlier colonoscopic

evaluation. As discussed in Section 2.4.2, further validation is required before polygenic risk scores can be routinely incorporated into clinical screening programs [118].

Also, the creation of non-invasive biomarkers is quite promising. Testing stool for *Flavonifractor plautii* DNA or particular methylation DNA markers that are different from those employed in current average risk tests could be a useful and scalable way to screen people under 45. Circulating microRNA panels offer a further non-invasive screening avenue; a three-miRNA signature comprising hsa-miR-20a-5p, hsa-miR-21-5p, and hsa-miR-210-3p has demonstrated strong discriminative performance for differentiating early- and advanced-stage CRC, supporting its potential as a minimally invasive biomarker panel for population-based screening [119]. Formal cost-effectiveness analyses of risk-adapted screening strategies in younger populations remain limited and will be necessary to inform policy adoption and resource allocation.

10.2. Therapeutic Implications

In the case of EO-CRC, precision oncology means going after both the tumour's particular genetic pathways and the environmental elements that make them work. Possible methods involve targeting the exposome by interventions that rectify metabolic imbalance, including the application of bile acid sequestrants or specialized probiotics aimed at displacing pks+ E. coli.

There seem to be a few routes that are especially important for younger individuals when it comes to tumour-specific therapy. The significant increase of MAPK signalling in EO-CRC, even in RAS wild-type tumours, indicates that clinical trials for MEK or ERK inhibitors should be prioritized for young patients with microsatellite stable (MSS) cancer [47]. Additionally, the dominance of the CMS2 subtype and canonical Wnt activation makes EO-CRC an attractive setting for investigating emerging Wnt pathway inhibitors, including porcupine inhibitors and beta-catenin disruptors. However, clinical translation of Wnt-targeted therapies remains challenging because Wnt signaling is essential for normal intestinal stem-cell maintenance and bone homeostasis. Early-phase trials of porcupine inhibitors and other Wnt pathway antagonists have reported dose-limiting toxicities including gastrointestinal injury, impaired mucosal regeneration, and reductions in bone mineral density. These findings highlight the narrow therapeutic window of Wnt inhibition and underscore the need for more selective approaches capable of targeting tumor-specific Wnt signaling while preserving normal tissue function. Complementing these synthetic Wnt-targeted agents, certain traditional Chinese medicine formulations have also been investigated for their capacity to modulate this pathway with a potentially more favourable safety profile; for example, BuShenFang was shown to upregulate adenomatous polyposis

coli (APC) expression while suppressing β-catenin, c-Myc, and Cyclin D1 in colorectal cancer cell lines, suggesting a complementary strategy for restoring Wnt/β-catenin pathway regulation in CRC [120].

Finally, the comparatively lower frequency of canonical RAS and BRAF V600E mutations in left-sided EO-CRC supports the potential efficacy of anti-EGFR antibodies such as cetuximab or panitumumab in appropriately selected patients, provided they do not possess rare non V600E *BRAF* mutations or *HER2* amplifications [121]. Future clinical trial design should also account for the unique biology of EO-CRC rather than treating younger patients as a simple extension of average-onset disease. Age-stratified enrollment strategies, incorporation of microbiome and metabolomic biomarkers, and endpoints relevant to younger populations, including fertility preservation, long-term functional outcomes, treatment-related quality of life, and survivorship burden, may improve the translational relevance of future studies. Given the molecular heterogeneity within EO-CRC, biomarker-driven adaptive trial designs may be particularly valuable for evaluating targeted therapies in CMS2-dominant, MSS, and metabolically dysregulated tumors. To facilitate clinical interpretation and highlight areas of greatest translational potential, the principal therapeutic strategies currently under investigation or clinical application in EO-CRC are prioritized according to their level of evidence and stage of clinical development (Table 8).

Table 8. Prioritization of Emerging Therapeutic Strategies in EO-CRC.

Therapeutic Strategy	**Target Population**	***Current Evidence Strength**	**Clinical Status**	**Future Clinical Trials**
Anti-EGFR therapy (cetuximab, panitumumab)	Left-sided, RAS wild-type, BRAF V600E wild-type EO-CRC	Strong	Established clinical practice	Already standard of care; EO-CRC-specific comparative and biomarker-refinement trials remain a research priority
MEK/ERK pathway inhibition	MSS, MAPK-activated EO-CRC	Moderate	Investigational; ongoing clinical trials	Prospective trials of MEK/ERK inhibitors enriched for MSS, MAPK-activated EO-CRC populations
Combination immunotherapy (VEGF, MEK, checkpoint blockade)	MSS/TMB-low EO-CRC	Moderate	Early clinical evaluation	Trials combining checkpoint blockade with VEGF or MEK inhibition specifically in MSS/TMB-low EO-CRC
Microbiome-targeted interventions	Microbiome-associated EO-CRC	Emerging	Preclinical/Early translational	Early-phase trials of microbiome-modulating agents paired with biomarker validation studies

Wnt pathway inhibitors	CMS2-dominant EO-CRC	Emerging	Preclinical/Early phase trials	Trials of selective Wnt pathway antagonists designed to limit intestinal and skeletal toxicity

*Evidence strength was categorized as Strong (established clinical efficacy), Moderate (supported by clinical trials but not yet standard of care), and Emerging (preclinical or early-phase evidence requiring validation).

10.3. Survivorship and Onco-Fertility

As survival rates remain relatively high due to the physiological resilience of younger patients despite advanced stages of the disease, clinical guidelines now place a significant emphasis on upfront fertility preservation. The biological and clinical reality of EO-CRC means that survivors may face several decades of life managing the long-term effects of treatment, such as oxaliplatin induced neuropathy and altered bowel function [2, 122]. Current oncology guidelines, including recommendations from the American Society of Clinical Oncology and the European Society for Medical Oncology, emphasize that fertility preservation discussions should occur as early as possible following cancer diagnosis and before initiation of potentially gonadotoxic treatment. Available options include sperm cryopreservation, oocyte or embryo cryopreservation, ovarian tissue preservation, and fertility-sparing reproductive counseling. Given the young age of many EO-CRC patients, timely referral to reproductive specialists should be considered a routine component of multidisciplinary care rather than an optional adjunct to treatment planning [123]. Consequently, onco-fertility counselling and the implementation of survivorship plans must be integrated into the initial treatment strategy rather than treated as a secondary concern. Beyond physical toxicities, younger survivors frequently experience substantial psychosocial burdens, including anxiety related to recurrence, career disruption, financial stress, altered body image, fertility concerns, and long-term impacts on social relationships. Consequently, multidisciplinary survivorship programs integrating psychological support, fertility counseling, nutritional guidance, and rehabilitation services are increasingly recognized as essential components of EO-CRC care [124]. These challenges underscore the importance of age-specific psychosocial support services, financial counselling to mitigate treatment-related financial toxicity, and structured return-to-work programmes as core components of comprehensive survivorship care for younger patients [124].

11. Conclusion

EO-CRC is increasingly recognized as a biologically distinct form of colorectal cancer with unique molecular, microbial, and clinical characteristics that differentiate it from traditional late-onset disease. Current evidence supports a multifactorial model in which

hereditary susceptibility, environmental exposures, microbial dysbiosis, and epigenetic alterations interact to drive tumorigenesis in younger individuals, with microbiome-host interactions increasingly recognized as a central and potentially targetable axis in this multifactorial process.

The rising global incidence of EO-CRC highlights the limitations of age-based approaches to prevention and diagnosis. Improved clinician awareness of red-flag symptoms, implementation of risk-adapted screening strategies, and broader integration of molecular risk factors will be essential to facilitate earlier detection and improve outcomes.

Among the most important emerging insights are the potential contributions of microbiome-associated carcinogenesis, exposure-related mutational processes such as colibactin-mediated DNA damage, and CMS2-dominant molecular biology. These findings provide new opportunities for biomarker development, early detection, and therapeutic intervention, although causal relationships and clinical utility require further validation.

Future progress will depend on integrating genomic, epigenetic, transcriptomic, metabolomic, and microbiome data into clinically applicable precision medicine frameworks. Development of EO-CRC-specific preclinical models, prospective multi-omics cohorts, and biomarker-guided clinical studies will be critical for translating biological discoveries into improved prevention, diagnosis, and treatment strategies for younger patients.

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