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Epigenetic dysregulation of gastrointestinal tumors

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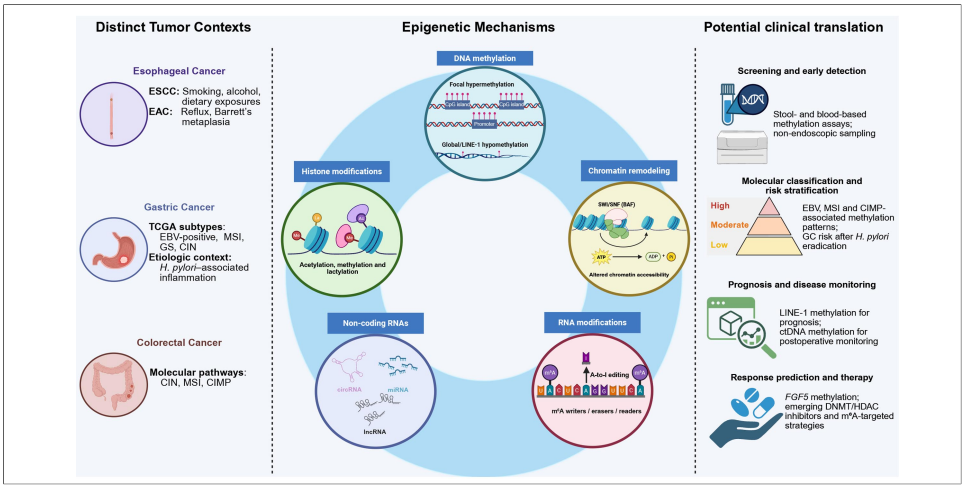

Abstract

Gastrointestinal cancers mainly include esophageal cancer, gastric cancer, and colorectal cancer. These tumor types account for a huge number of new cases and deaths across the world. Although numerous genetic studies have shown the importance of gene mutations in their pathology, they are still insufficient to capture all layers of cancer development. Recently, epigenetic dysregulation has drawn attention because of its potential in the diagnosis and treatment of gastrointestinal cancers. Among diverse epigenetic pathways, DNA methylation is the best-studied and has displayed clinical value. Additionally, research on histone modifications, chromatin remodeling and RNA-mediated regulation is rapidly accumulating. In this review, we systematically illustrate the epigenetic dysregulation in gastrointestinal cancers to provide hints for clinical transformation.

INTRODUCTION

Gastrointestinal cancers are among the cancer types with the highest incidence and mortality rates worldwide. According to the 2022 global cancer statistics (GLOBOCAN), esophageal cancer (EC), gastric cancer (GC), and colorectal cancer

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(CRC) rank as the most prevalent and lethal gastrointestinal malignancies, raising a major challenge to global public health[1,2]. Notably, gastrointestinal malignancies also encompass liver cancer, pancreatic cancer, and biliary tract cancer. However, in this review, the terms EC, GC, and CRC are used to refer to the gastrointestinal tract malignancies that share a common mucosal epithelial origin.

In 2022, there were 4.906 million new cases of gastrointestinal tumors, accounting for 24.6% of all new cancer cases worldwide[1]. Among them, CRC is the most common tumor, which ranks third in incidence and second in mortality globally, leading to approximately 1.9 million new cases and 0.9 million deaths[3]. Additionally, GC accounts for about 0.97 million new cases and 0.66 million deaths annually, ranking as the fifth most common cancer and the fourth leading cause of cancer death worldwide[4]. Meanwhile, EC has approximately 0.511 million new cases and 0.445 million deaths annually, with five-year survival rates as low as 20%[5]. Moreover, the disease burden of gastrointestinal tumors is expected to increase further by 2050, with approximately 9.06 million new cases and 6.42 million deaths annually, showing a rapidly increasing trend[6]. Strikingly, these tumors are especially prominent in Asia, and particularly in East Asia. There were approximately 0.517 million new CRC cases and 0.24 million CRC deaths reported in China in 2022[3]. Additionally, new cases and deaths of EC in China accounted for 44% and 42% of the global number, respectively[7].

To develop effective therapies for these gastrointestinal cancers, it is critical to understand their genetic basis. However, considerable evidence indicates that genetic models based solely on DNA sequence alterations cannot fully explain the initiation, progression, and heterogeneity of gastrointestinal tumors. Instead, epigenetic alterations function as another layer of cancer regulation. Epigenetic regulation refers to the mechanisms by which gene expression is modulated without altering DNA sequence. The main layers include DNA methylation, post-translational histone modifications, Adenosine Triphosphate (ATP)-dependent chromatin remodeling, and RNA-mediated regulatory mechanisms. Recent studies revealed that these mechanisms play important roles in gastrointestinal tumor development, shifting the research focus from a purely genetic perspective toward the broader field of epigenetics. This review introduces the epigenetic alterations associated with gastrointestinal cancers and discusses their potential applications in clinical diagnosis and treatment.

EPIGENETIC REGULATION SHAPES TUMOR BIOLOGY

Epigenetic regulation shapes transcriptional states and cell identity without changing the primary DNA sequence. Epigenetic dysregulation is associated with various diseases, such as osteoporosis[8], nervous system diseases[9], and cancers[10]. Importantly, these changes are often mitotically heritable, but many are also potentially reversible. This reversibility forms the basis for their potential in cancer treatment. While genetic lesions classically initiate oncogenesis by activating oncogenes or repressing tumor suppressors, the epigenetic landscape contributes to tumorigenesis either dependent or independent of genetic alteration. Additionally, epigenetic dysregulation also impacts how malignant cells acquire lineage plasticity, evade microenvironmental stress, and resist therapeutic pressure. Importantly, these epigenetic mechanisms rarely act independently. Instead, changes in one epigenetic layer often influence other layers, collectively shaping cancer-associated transcriptional states. In gastrointestinal malignancies, this epigenetic network operates within tissues impacted by epithelial renewal, inflammation, microbiota, diet-related exposures, and toxic injury, resulting in epithelial-mesenchymal transition (EMT), metastatic dissemination, and therapy resistance[11,12].

DNA methylation is the most extensively characterized epigenetic layer in cancer biology. In malignant transformation, the methylation landscape is usually disrupted in two directions. On the one hand, promoter CpG island hypermethylation can silence tumor suppressor genes, DNA repair components, and

differentiation programs. On the other hand, global DNA hypomethylation can destabilize repetitive elements and pericentromeric regions, contributing to chromosomal instability, structural variation, and aberrant activation of normally silenced retrotransposons. The clinical relevance of these changes is clearest in selected settings. For instance, *MLH1* promoter hypermethylation is a major mechanism of mismatch-repair deficiency and microsatellite instability in sporadic CRC[13]. Also, *MGMT* promoter hypermethylation impairs DNA repair and is associated with benefit from temozolomide in glioblastoma[14]. These examples explain why DNA methylation is useful both as a disease mechanism and as a stratification marker. Therefore, DNA methylation should not be regarded as a uniform process, since focal and global methylation changes can have different biological consequences.

Histone modifications impact chromatin condensation and recruit effector proteins that determine whether regulatory elements are active, poised, or repressed. Active promoters are often marked by H3K4me3, while polycomb-repressed regions are commonly associated with H3K27me3[15]. Cancer studies have shown that this layer is not merely correlative. Recurrent EZH2 Tyr641 mutations in germinal-center-derived follicular lymphoma and diffuse large B-cell lymphoma alter Polycomb Repressive Complex 2 (PRC2) activity. As a result, H3K27me3-associated chromatin states and malignant differentiation programs are reshaped[16].

Histone modifications also interact with ATP-dependent chromatin remodeling complexes. The SWItch/Sucrose NonFermentable (SWI/SNF) (also called BAF) machinery can slide, evict, or restructure nucleosomes and change transcription-factor access to enhancers and promoters. Inactivation of core subunits can therefore have broad regulatory effects. For example, frequent ARID1A mutations in ovarian clear cell carcinoma rewire enhancer landscapes, disrupt three-dimensional regulatory loops, and allow malignant cells to change lineage identity or acquire phenotypic plasticity[17,18].

Non-coding RNAs add another route through which epigenetic programs are regulated. Long non-coding RNAs (lncRNAs) can act as molecular scaffolds that guide chromatin regulators to specific genomic loci[19]. Their dysregulation is associated with tumor development, metastasis, and drug resistance. *HOTAIR* is a well-known example that recruits PRC2, reprograms the chromatin state, and promotes metastatic dissemination in breast cancer[20]. Other RNA classes act through different mechanisms. MicroRNAs fine-tune oncogenic or tumor-suppressive networks after transcription, whereas circular RNAs can sequester microRNAs or modulate nuclear protein interactions[21].

Covalent RNA modifications, especially N^6-methyladenosine (m^{6}A), can influence transcript stability, processing, and translation efficiency. In acute myeloid leukemia, promoter-bound METTL3 deposits m^{6}A marks on oncogenic transcripts and enhances their translation[10]. This example illustrates how RNA-centered regulation can cooperate with chromatin states to sustain malignant phenotypes. Some epigenetic regulators may create druggable vulnerabilities in selected tumor contexts given their roles as enzymes or specialized protein-interaction hubs. Overall, epigenetic pathways synergistically impact tumor progression, plasticity, immune evasion and therapeutic resistance. Figure 1 summarizes the major epigenetic mechanisms and their functional links to tumor progression, plasticity, immune evasion and therapeutic resistance.

EPIGENETIC REGULATION IN ESOPHAGEAL CANCER

Esophageal mucosa is repeatedly exposed to mechanical trauma, dietary carcinogens, microbial populations, and chronic inflammatory reflux. Therefore, EC is a useful setting for examining how environmental injury interacts with epigenetic reprogramming. EC includes two major histological and etiological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). They differ in epidemiology, risk factors, precursor lesions, and molecular background[22]. They share overlapping classes of

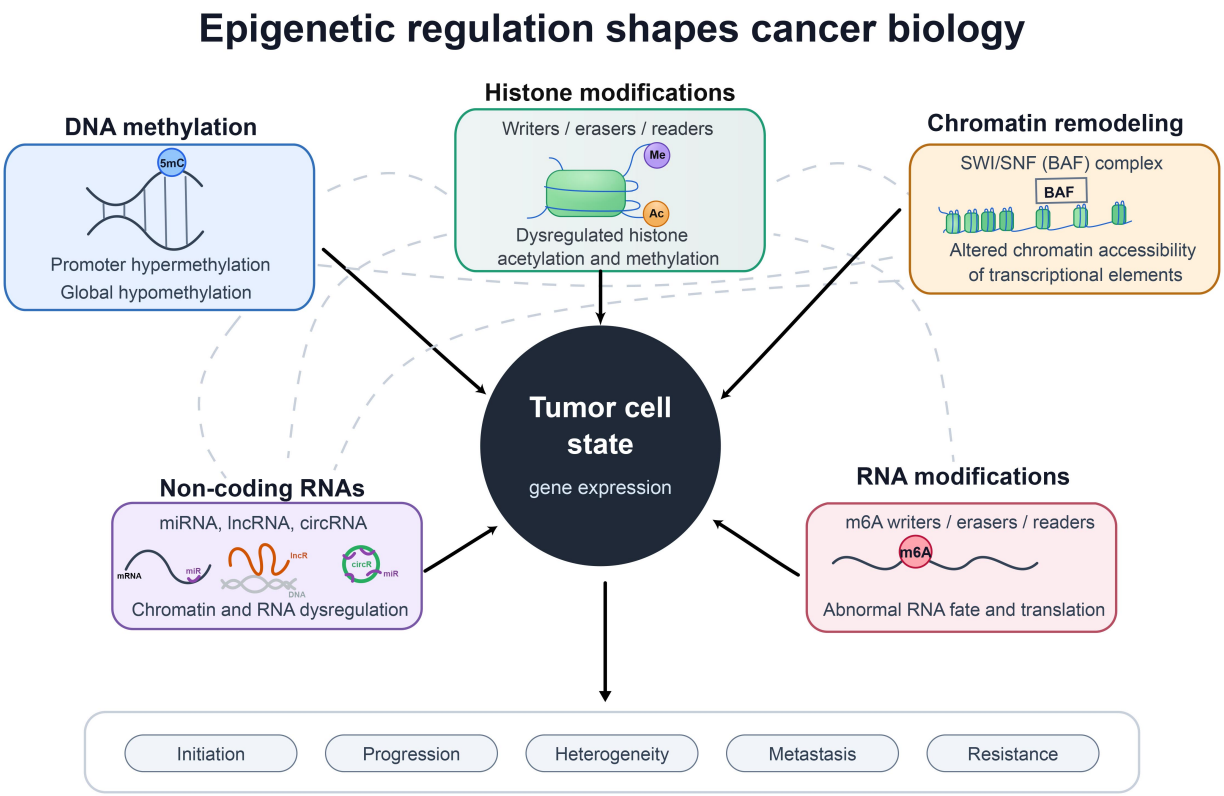

Figure 1. Epigenetic dysregulation shapes tumor biology. Five major epigenetic layers (DNA methylation, histone modifications, chromatin remodeling, non-coding RNAs, and RNA modifications) collectively influence tumor cell state and gene expression. Solid arrows indicate direct contributions to clinical trajectories (e.g., progression, metastasis, and resistance). Gray dashed lines highlight the extensive cross-talk among these layers, illustrating how alterations in one mechanism actively reshape others to drive oncogenesis. miRNA: MicroRNA; lncRNA: long non-coding RNA; circRNA: circular RNA; BAF: BRG-/BRM-associated factor.

epigenetic machinery, but within distinct cellular and developmental trajectories.

DNA methylation abnormalities and biomarkers in ESCC

In ESCC, aberrant DNA methylation is the most mature epigenetic hallmark. Large-scale epigenomic studies have identified widespread methylation alterations that correlate with patient outcomes[23-25]. Genome-wide hypomethylation often affects repetitive elements, including long interspersed nucleotide sequences (LINE-1). This pattern has been associated with chromosomal instability and poor prognosis after curative tumor resection[24,26]. Moreover, global methylation loss coexists with localized promoter CpG island hypermethylation, which can silence regulatory loci. One example is hypermethylation-mediated silencing of the tumor suppressor *SEMA3B* and its antisense lncRNA *SEMA3B-AS1*, which has been associated with ESCC progression and unfavorable survival[27].In addition, multi-region methylation profiling has revealed both intertumor and intratumor methylation heterogeneity in ESCC. This heterogeneity correlates with lymph node metastasis, suggesting that subclonal epigenetic diversification may accompany selection of more aggressive tumor-cell populations[28].

Research on DNA methylation biomarkers in ESCC is also expanding rapidly. For instance, CDH1 promoter hypermethylation is observed in 43% of ESCC patients and is associated with recurrence of early-stage ESCC[29]. Also, the association between ESCC and promoter hypermethylation of DNA damage repair genes, such as *MGMT* and *MLH1*, has been well studied[30,31]. Additionally, targeted bisulfite sequencing has generated multi-gene methylation panels for ESCC detection and identified several genomic regions that were able to act as biomarkers, including regions covering *STK3* and *ZNF418*[32]. Locus-specific

hypermethylation, including *FGF5* promoter methylation, has been reported as a candidate marker of sensitivity to definitive chemoradiotherapy[33]. These findings highlight their clinical potential, but careful validation across independent cohorts, sample types, and treatment settings remains necessary.

Histone modification, chromatin remodeling, and RNA-mediated regulation in ESCC

Histone-modifying enzymes and structural chromatin states provide further mechanistic insight into ESCC pathogenesis. The available evidence is more pathway-specific than that for DNA methylation, but several studies support its functional relevance. The histone demethylase JMJD3 promotes ESCC pathogenesis through epigenetic regulation of MYC proto-oncogene (MYC)[34]. Histone modifiers can also cooperate with transcriptional regulators to repress expression of non-coding RNAs. For example, SOX4 recruits EZH2 and Histone deacetylase 3 (HDAC3) to the miR-31 promoter, thereby silencing miR-31 expression and promoting an invasive cellular phenotype[35]. In addition, super-enhancer remodeling contributes to oncogenic transcription in ESCC. Active H3K27 acetylation (H3K27ac) can activate the lncRNA *CCAT1*, which coordinates *SPRY4* and *HOXB13* expression, resulting in ESCC migration and proliferation[36].

At the architectural level, chromatin remodeling complexes appear to be disrupted early during squamous carcinogenesis. Somatic mutations in SWI/SNF complex subunits have been reported as early events in esophageal squamous carcinogenesis[37]. Furthermore, loss or downregulation of the core SWI/SNF subunit ARID1A is associated with infiltrative growth in established ESCC tumors[38]. These structural changes usually intersect with lineage-specific transcriptional programs. The squamous transcription factors TP63, SOX2, and KLF5 form a core regulatory circuitry that binds open, hyper-accessible chromatin regions and reshapes enhancer usage[39]. Chromatin accessibility profiling has also identified hyper-accessible enhancers and enhancer RNAs in ESCC cells, including a putative enhancer-derived enhancer RNA (eRNA) for Epidermal Growth Factor Receptor (EGFR)[40].

Evidence for non-coding RNAs and m^{6}A RNA modifications in ESCC is growing, but it remains immature. Interestingly, some ncRNAs not only act as downstream effectors, but also influence chromatin-modifying complexes or DNA methylation directly. The lncRNA *POU3F3*, for example, promotes DNA methylation in ESCC cells[41]. Similarly, circIMMP2L promotes malignant progression by securing nuclear retention of the transcriptional corepressor CtBP1 and modulating downstream epigenetic modifications[42]. Moreover, m^{6}A RNA modification extends another epigenetic layer to ESCC cell-state control. The key point is not simply the presence of m^{6}A marks, but their dynamic deposition and removal on mRNA transcripts. The m^{6}A demethylase ALKBH5 suppresses esophageal cancer malignancy by regulating primary microRNA biogenesis and *RAI1* expression[43]. METTL14, a critical m^{6}A methylase, participates in a positive feedback loop with miR-99a-5p and TRIB2 in radioresistant ESCC cell populations. This circuit recruits HDAC2, sustains a cancer stem cell phenotype, and promotes radioresistance[44]. These molecule-specific mechanisms broaden the biological view of ESCC plasticity. However, the breadth of clinical validation available for RNA methylation biomarkers remains inadequate.

Epigenetic alterations in EAC and Barrett's-associated progression

EAC has a different epigenetic context from ESCC. Its epigenetic landscape is closely linked to the inflammatory and metaplastic trajectory of Barrett's esophagus. In this glandular lineage, widespread DNA hypomethylation occurs early in the premalignant metaplastic stage. It may also synergize with focal gene amplification during progression toward adenocarcinoma[45]. Importantly, DNA methylation profiling has delineated molecular subclasses across Barrett's esophagus and EAC[46]. This classification becomes more informative when methylation profiles are integrated with transcriptomic and genomic data[47]. One subtype-associated event is hypermethylation-mediated downregulation of *NDRG4*, a tumor-suppressive gene in EAC[48]. Meanwhile, chromatin-level studies suggest that global accessibility shifts can establish a hybrid

stomach-intestinal chromatin state that underlies metaplastic cellular reprogramming in human Barrett's tissue[49].

Overall, DNA methylation and localized chromatin states provide the strongest epigenetic evidence base for EAC progression. Direct evidence for EAC-specific histone modifiers, lncRNA scaffolds, and m^{6}A RNA-modification pathways remains comparatively sparse. This imbalance matters for interpretation. ESCC and EAC share broad epigenetic mechanisms, but they deploy them within distinct lineage and developmental contexts. This distinct lineage context underscores the need to evaluate epigenetic mechanisms in ESCC and EAC independently, despite their shared molecular machinery.

Clinical translation of epigenetic markers in esophageal cancer treatment

Clinical translation remains limited and differs by histological subtype. No epigenetic biomarker or epigenetic drug is established in the routine management of ESCC. The DNA methylation panels, LINE-1 methylation, and *FGF5* methylation remain candidate tissue markers that require prospective assay validation. In Barrett's esophagus and EAC, non-endoscopic cell collection coupled to methylated *VIM* and *CCNA1* testing has progressed. The EsoGuard assay has been analytically validated as a CLIA/CAP laboratory-developed test using samples collected with the FDA-cleared EsoCheck device[50]. However, analytical validation alone does not establish population-level clinical utility. The 2022 American College of Gastroenterology (ACG) guideline found insufficient evidence to recommend routine biomarker panels. Therefore, positive molecular tests still require a confirmatory endoscopy[51]. In addition, azacitidine priming has entered early-phase evaluation in resectable gastric and esophageal adenocarcinoma. However, neither DNA methyltransferase nor histone deacetylase inhibitor is used as standard treatment for ESCC or EAC[52]. Future studies should prioritize prospective validation in well-defined risk populations, particularly for ESCC-specific methylation markers, where tumor heterogeneity and the lack of standardized assays remain major barriers to clinical implementation.

EPIGENETIC DYSREGULATION IN GASTRIC CANCER

GC remains a major cause of cancer morbidity and mortality worldwide. Its development reflects long-standing mucosal injury, exposure to microbes and viruses, genetic changes that are either inherited or acquired, and changes in the regulation of chromatin and RNA[53,54]. Epigenetic alterations are especially relevant in the stomach because they are not confined to established tumors. They can be detected in non-neoplastic mucosa and can accumulate during metaplasia and dysplasia, thus helping define tumor subgroups. In the Cancer Genome Atlas Program (TCGA) classification, GC is divided into Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomically stable, and chromosomal instability subtypes. Among them, EBV-positive tumors show extensive CpG island hypermethylation, whereas MSI tumors often involve methylation-associated mismatch-repair deficiency[55].

DNA methylation abnormalities in GC

DNA methylation is the best-characterized epigenetic alteration in GC. Two broad patterns are repeatedly described: focal CpG island promoter hypermethylation and global hypomethylation. As observed in EC, promoter hypermethylation can silence tumor-suppressive or DNA-repair genes, whereas global hypomethylation often affects repetitive elements and may contribute to chromosomal instability and retrotransposon activity[56-58]. Notably, genome-wide methylation studies have identified methylation-defined GC subgroups, indicating that DNA methylation functions both as a gene-specific regulatory event and as a tumor-classification feature[55,59].

The EBV-positive and MSI subtypes illustrate two clinically recognizable methylation patterns. EBV-positive GC shows extensive CpG island hypermethylation, a feature that helps distinguish it from other molecular subtypes[55]. In MSI tumors, promoter methylation of mismatch-repair genes, particularly *MLH1*, leads to

mismatch-repair deficiency and microsatellite instability[55]. These subtype-linked methylation patterns are useful because they link epigenetic alterations to established molecular classifications rather than treating GC as a single disease.

Helicobacter pylori infection provides another gastric cancer-specific link between inflammation and DNA methylation. Aberrant methylation can be detected in *H. pylori*-infected noncancerous gastric mucosa, supporting an epigenetic defect model in which histologically non-malignant tissue already carries cancer-associated methylation changes[60]. This effect has practical implications. Methylation-based markers have been tested to stratify the risk of primary GC after *H. pylori* eradication, including in high-risk individuals who remain under endoscopic surveillance[61]. This epigenetic defect model separates GC-specific DNA methylation biology from a purely tumor-centered view. The methylation signal in noncancerous mucosa may reflect previous inflammatory injury, persistent epithelial remodeling, or selection of altered epithelial clones. This explains why risk remains measurable after *H. pylori* clearance: although eradication removes the inflammatory stimulus, it does not necessarily erase the accumulated methylation changes[60,61].

At the gene level, promoter hypermethylation has been reported in cell-cycle regulators, DNA-repair genes, adhesion-related genes, and apoptosis-associated genes, including *CDKN2A*/p16INK4a, *MLH1, MGMT*, *CDH1,* and *CASP8*[62-66]. LINE-1 hypomethylation in upper gastrointestinal cancers has been associated with increased retrotransposition and tumor-specific insertions, providing a plausible connection between global hypomethylation and genomic instability[56]. In GC models, DNA hypomethylation can also promote invasive behavior by regulating SP1 binding at the *CDCA3* promoter[67]. Taken together, abnormal DNA methylation patterns in GC and noncancerous gastric mucosa shed light on its clinical applications.

Histone modification and chromatin remodeling in GC

Compared with DNA methylation, research on histone modifications in GC has focused on specific mechanisms. For instance, EZH2, the catalytic subunit of PRC2, mediates H3K27 trimethylation and drives gastric tumorigenesis by silencing tumor suppressor genes[68-71]. Furthermore, EZH2 can interact with the DNA methylation machinery, suggesting that polycomb-mediated repression and promoter methylation often cooperate to silence target genes[69].

Other chromatin regulators appear to act in more restricted settings. Inhibition of the lysine demethylase KDM4C induces senescence in *TP53*-mutant GC cells, suggesting that dependency on histone demethylases may vary by genetic background[72]. Chromatin remodeling defects show a similar subtype bias. The BAF subunit ARID1A is frequently altered in subsets of GC, especially MSI and EBV-associated tumors, and TCGA identified ARID1A among the most recurrent chromatin-regulatory alterations[55,73]. These findings indicate that chromatin remodeling in GC is highly subtype-specific, rather than a general process across all tumors.

Non-coding RNAs, RNA editing and m^{6}A RNA modification in GC

Non-coding RNA studies in GC cover many molecules and phenotypes, so the evidence is less uniform than that for DNA methylation. Several miRNAs have been linked to drug response, tumor progression, or biomarker potential. For example, miR-27a has been associated with HIF-1α-related multidrug resistance, whereas miR-215/192 and miR-148a-3p have been reported in GC progression and biomarker studies[74-76]. LncRNAs and circRNAs have also been widely studied. For instance, *HOTAIR* is linked to cisplatin resistance and histone-mark switching during the epithelial-mesenchymal transition[77]. Additionally, *MALAT1* promotes tumor progression via a miRNA-associated axis, while *circAKT3* and *circPVT1* are implicated in cisplatin resistance, proliferation, and prognostic stratification[78-81]. However, compared with DNA methylation alterations, evidence supporting ncRNA-based mechanisms in GC remains less consistent.

RNA editing provides a distinct post-transcriptional mechanism. ADAR-mediated A-to-I RNA editing is altered in GC and has been associated with disease progression and prognosis, with ADAR1 overexpression and ADAR2 downregulation contributing to an editing imbalance in tumor tissues[82]. CPEB3 has also been reported to suppress GC progression partly through regulation of ADAR1 mRNA localization and ADAR1-mediated RNA editing[83].

m^{6}A RNA modification is an emerging area in GC research. METTL3 has been reported to promote GC proliferation, migration, epithelial-mesenchymal transition, and MYC-associated transcriptional programs[84,85]. The m^{6}A reader YTHDF1 can promote gastric carcinogenesis by enhancing translation of *FZD7* and activating Wnt/β-catenin signaling[86]. These findings support a role for m^{6}A-mediated post-transcriptional control, but most data still come from mechanistic studies rather than prospective clinical cohorts.

Clinical translation of epigenetic markers in GC treatment

Clinical use of epigenetic information in GC remains indirect. MSI status is incorporated into clinical biomarker assessment and treatment selection, whereas EBV status is mainly used for molecular or pathological classification in selected settings. These features are generally assessed by immunohistochemistry, MSI testing, sequencing, or Epstein-Barr Virus Early RNA (EBER) *in situ* hybridization rather than by methylation assay[87]. The extensive CpG island hypermethylation of EBV-positive tumors and *MLH1*-associated methylation in MSI tumors are therefore biologically and taxonomically important but are not routine stand-alone clinical tests. RIMS1 methylation measured in non-neoplastic antral and body biopsies is undergoing prospective validation for risk stratification after *H. pylori* eradication[61]. However, external validation, assay standardization, and incorporation into surveillance algorithms are still required. Overall, DNA methylation currently represents the most clinically advanced epigenetic approach in GC, whereas histone modifications, ncRNAs, and m^{6}A-related biomarkers remain largely investigational. Further prospective studies with standardized assays and clinically relevant endpoints are required before these emerging markers can be incorporated into routine clinical practice.

EPIGENETIC REGULATION IN COLORECTAL CANCER

CRC is probably the most well-documented gastrointestinal tumor. Based on its Consensus Molecular Subtypes (CMS), it is divided into four subtypes (CMS1-4). On the other hand, CRC pathogenesis is driven by three major molecular mechanisms: chromosomal instability (CIN, ~85% of cases), microsatellite instability (MSI, ~15% of cases), and the CpG island methylator phenotype (CIMP, ~20% of cases). Notably, CIMP-high tumors frequently overlap with MSI-high or Recombinant B-Raf Proto Oncogene Serine/Threonine Protein Kinase (BRAF)-mutant tumors. These pathway-based features are distinct from, yet complementary to, the CMS classification. The classic adenoma-carcinoma sequence model proposed by Fearon and Vogelstein emphasized the sequential accumulation of genetic mutations in *APC*, *KRAS*, and *TP53*[88]. However, genetic alterations alone cannot fully account for the heterogeneity, plasticity, and clinical behavior of CRC. Over the past two decades, growing evidence has demonstrated that epigenetic dysregulation plays a critical driving role in CRC initiation, progression, metastasis, and therapeutic resistance.

DNA methylation in CRC

Aberrant DNA methylation is a hallmark of CRC, manifesting both as genome-wide hypomethylation and as locus-specific hypermethylation of promoter CpG islands. The CIMP defines a distinct subset of CRCs characterized by simultaneous hypermethylation of multiple loci. In a large cohort analysis of 295 sporadic CRCs, Toyota and colleagues first identified CIMP-high tumors, accounting for approximately 20% of cases[89]. Subsequent studies have established the clinical relevance of CIMP. For instance, CIMP-high tumors

are associated with *BRAF* mutations, proximal colon location, and high-level MSI[90]. In terms of prognosis, CIMP-high status generally predicts worse overall survival[91,92]. Notably, this prognostic effect is possibly context-dependent. Some studies reported that CIMP-high confers higher mortality among microsatellite-stable cancers, but not MSI-high cancers[93].

Beyond global CIMP status, hypermethylation of individual tumor suppressor gene promoters occurs early in colorectal tumorigenesis. A comprehensive analysis including colorectal adenomas and carcinomas showed that promoters of *APC*, p16/*CDKN2A*, and *RASSF1A* are already methylated in adenomas at frequencies comparable to those seen in carcinomas[94]. Even in aberrant crypt foci, the earliest histologically identifiable lesions, hypermethylation of *APC* can be detected and correlates with reduced gene expression[95]. Similarly to other gastrointestinal tumors, methylation of DNA repair gene promoters, including *MGMT*, *MLH1*, and *MSH2*, has been linked to CRC carcinogenesis[94,96]. Genome-wide methylation sequencing has further expanded the list of frequently methylated genes in CRC, including *NDRG4*, *BMP3*, *MFAP2*, *APOL3*, *RNASEL*, *SFRP1*, and *SFRP2*, all of which distinguish cancer from normal tissue with high sensitivity[97,98]. To clarify their clinical use, combining machine learning and integrated analysis of TCGA DNA methylation signatures with comorbidity patterns revealed that a three-gene panel of *ADHFE1*, *ADAMTS5,* and *MIR129-2* achieved the best CRC classification performance among ten candidate genes[99]. In terms of prognosis, p16/*CDKN2A* promoter hypermethylation is present in about one-third of tumors and is associated with loss of p16 expression, thus correlating with shorter patient survival[95,100]. Collectively, these studies establish DNA methylation as an early and heterogeneous feature of colorectal tumorigenesis and provide the biological basis for molecular classification and biomarker development.

The clinical application of DNA methylation biomarkers has been extensively validated in non-invasive settings. For plasma-based screening, a prediction model including five blood leukocyte DNA methylation markers for detecting colorectal neoplasms reached excellent performance with an area under the curve (AUC) of 0.85, which can further improve to 0.89 by combining with a lifestyle risk score[101]. More recently, circulating tumor DNA (ctDNA) methylation haplotypes have emerged as powerful prognostic tools. The ColonES assay, developed by a multicenter study, detects methylation haplotypes across 191 genomic regions, predicting CRC with 86% sensitivity and advanced adenoma with 79% sensitivity[102]. Importantly, patients with high preoperative ctDNA methylation scores had significantly shorter relapse-free and overall survival[102]. Additionally, methylation of *BCAT1* and *IKZF1* in plasma ctDNA frequently occurred in CRC and rapidly reversed after surgical resection, thus can inform adequacy of surgical resection[103]. Using a single-tube multiplex qMSP assay for six methylation markers, Zhu and colleagues reported a specificity of 98.2% for CRC detection with sensitivity of 67.5 %[104]. Strikingly, highly methylated ctDNA levels were significantly associated with shorter relapse-free and overall survival[104]. Collectively, these findings suggest DNA methylation is critical to CRC generation and development and already displays remarkable potential in clinical diagnosis.

Histone modifications and chromatin accessibility in CRC: from initiation to therapy resistance

Although the roles of histone modifications in CRC are not as well developed as DNA methylation, their dysregulation contributes to every stage of CRC pathogenesis. Regarding tumor initiation, the H3K36 methyltransferase SETD2 acts as a tumor suppressor, whose mutation is frequent in CRC[105]. In a conditional knockout mouse model crossed with $Apc^{Min/+}$ mice, SETD2 loss increased the number of intestinal polyps by 3.5-fold and promoted progression to adenocarcinoma[106]. For CRC progression, the H3K9 methyltransferase SUV39H2 is significantly elevated in tumor tissues, and its high expression correlates with distant metastasis and poor survival[107]. Conversely, the H3K9 demethylase JMJD2C is overexpressed in liver metastases compared to primary tumors[108]. Mechanistically, JMJD2C binds the *MALAT1* promoter, reduces repressive H3K9me3 and H3K36me3 marks, and therefore upregulates *MALAT1* expression, which in turn

enhances β-catenin signaling and promotes metastasis in mouse models[108]. An emerging modification, histone lactylation, links metabolism to epigenetics. In *KRAS*-mutant CRC tissues, lactate accumulation drives histone H3 lysine 9 lactylation (H3K9la). ChIP-seq revealed that H3K9la is enriched at the *GRAMD1A* promoter, a cholesterol transporter gene. Knockdown of *GRAMD1A* suppresses proliferation and migration in *KRAS*-mutant cells, identifying H3K9la as a key mediator of KRAS-driven tumorigenesis[109].

Chemoresistance is a major clinical challenge, and histone acetylation plays a central role. HDAC3 mediates 5-fluorouracil resistance by directly deacetylating p21, thereby promoting its ubiquitination and degradation[110]. Treatment with the HDAC3 inhibitor restored p21 acetylation and stability and re-sensitized resistant cells to 5-FU[110]. Similarly, HDAC6 is overexpressed in chemoresistant CRC cells, and its selective inhibitor ACY1215 synergizes with chemotherapy to increase apoptosis and inhibit proliferation[111,112]. Besides HDACs, histone acetylase p300 is elevated in a substantial proportion of CRCs, acting as an oncogene through enhancing H3K27 acetylation and activating β-catenin[113].

Chromatin accessibility dynamics have been mapped at single-cell resolution. Using single-cell ATAC-seq on 48 polyps, 27 normal tissues, and 6 CRCs, researchers identified a continuum of chromatin remodeling from normal stem cells through polyps to cancer, characterized by progressive loss of differentiation-associated transcription factor motifs and gain of proliferation-associated motifs[114]. In the context of metastasis, CRC cells lose colon-specific accessible sites and instead gain accessibility at HNF4A binding sites[115]. Overall, histone modification and chromatin accessibility are critical epigenetic pathways in CRC, spanning tumorigenesis, proliferation, metastasis, and drug resistance. Although these findings indicate the clinical potential of therapy targeting histone modifications, there is a lack of solid evidence to support the application of enzyme- or pathway-specific inhibitors.

RNA-mediated regulation in CRC

LncRNAs and circRNAs function as key regulators of gene expression in CRC. *HOTAIR* is one of the most extensively studied lncRNAs in CRC. *HOTAIR* expression was higher in tumors from patients who developed liver metastasis, and its overexpression increased cell invasion significantly[116]. Mechanistically, *HOTAIR* binds to PRC2 and promotes H3K27me3-mediated silencing of metastasis suppressor genes[116]. Another lncRNA, *MALAT1*, is elevated in metastatic CRC and facilitates tumor progression by upregulating PI3K/Akt/mTOR and Wnt pathways[117,118]. In addition, circular RNAs, characterized by their covalently closed structure and high stability, often act as microRNA sponges. *CircCCDC66* is upregulated more than 8-fold in CRC tissues; its knockdown reduces tumor proliferation, migration, and invasion[119]. In the context of drug resistance, hsa_circ_0020095 is markedly elevated in cisplatin-resistant CRC cells, and it sponges miR-487a-3p to upregulate SOX9, accelerating cell proliferation and drug resistance[120].

In terms of RNA modification, an integrative analysis of 583 CRC patients from TCGA and Gene Expression Omnibus (GEO) cohorts, examining 20 m^{6}A regulators, identified two distinct clusters with significantly different overall survival[121]. Furthermore, m^{6}A-associated gene signatures were constructed and validated as independent prognostic predictors[121]. Additionally, METTL3 is elevated in nearly two-thirds of tumors and predicts poor survival[122]. Mechanistically, METTL3 methylates the 3'UTR of *MYC* mRNA, increasing its stability and protein levels[123,124]. These findings support a role for m^{6}A-associated RNA regulation in CRC biology, but therapeutic translation remains at an early stage.

Overall, epigenetic dysregulation is a driving force in colorectal cancer pathogenesis. DNA methylation signatures provide the most abundant insights in tumor pathology, serving as robust biomarkers for early detection, prognosis, and treatment prediction. Moreover, they have been applied in clinical settings with acceptable accuracy and sensitivity. However, more cautious validation across multiple centers and distinct

molecular subtypes is still necessary. Histone modifications and chromatin accessibility orchestrate critical processes underlying tumor initiation, progression, metastasis, and acquired drug resistance. Importantly, although some histone modification-based therapies have shown potential in CRC clinical treatment, they still need large-scale validation in patients across tumor stages and subtypes before clinical implementation. Additionally, it is not entirely clear how individual pathways function and how they form a network in this process. Finally, ncRNAs, including *HOTAIR*, *MALAT1*, and *circCCDC66*, function as key regulators of chromatin modification and miRNA sponging. Emerging RNA modifications m^{6}A add post-transcriptional control layers that influence prognosis and metabolism.

Clinical translation of epigenetic markers in CRC treatment

CRC has the most established clinical use of epigenetic testing among the cancers reviewed. For stool-based screening, multitarget DNA/Fecal Immunochemical Test (FIT) assays incorporate methylated DNA markers and are included among recommended screening strategies, while positive results require diagnostic colonoscopy[125,126]. For blood-based screening, the methylated SEPT9 test achieved ~75% sensitivity at 87% specificity for CRC detection[127]. Nonetheless, it has a restricted US regulatory indication for average-risk adults aged 50 years or older who have not completed other recommended screening, and it should not be presented as a replacement for first-line screening or colonoscopy[128]. In MLH1/PMS2-deficient tumors, *MLH1* promoter methylation is used as a cascade test, along with BRAF V600E, to support a sporadic origin and triage germline evaluation for Lynch syndrome[129]. A cell-free DNA assay incorporating genomic and epigenomic signals received US approval in 2024, although its sensitivity for advanced precancerous lesions was substantially lower than for CRC[130,131]. By contrast, ctDNA methylation assays for postoperative monitoring and inhibitors of DNA methyltransferases or histone deacetylases still require validation. A phase II trial of pembrolizumab plus azacitidine showed limited activity in refractory metastatic CRC[132]. Overall, DNA methylation represents the most clinically mature epigenetic layer in CRC, with established applications in screening and molecular classification, whereas histone modifications, chromatin remodeling, ncRNAs, and RNA modifications remain primarily at the investigational stage.

CONTEXT-DEPENDENT EPIGENETIC DYSREGULATIONS IN GASTROINTESTINAL CANCERS

Esophageal, gastric, and colorectal cancers involve the same broad classes of epigenetic regulation, but the biological consequences of these alterations depend on tissue lineage, etiological exposure, and precursor state. Figure 2 illustrates this cross-cancer epigenetic framework. ESCC develops in a squamous lineage associated with smoking, alcohol, and dietary carcinogens, whereas EAC is linked to reflux, Barrett's metaplasia, and glandular reprogramming. GC includes inflammation-associated methylation in non-neoplastic mucosa, distinct EBV-positive and MSI molecular subtypes. CRC develops through conventional adenoma-carcinoma pathways, and has the most established framework linking CIMP, mismatch-repair deficiency, and non-invasive molecular screening[55,88,133]. Table 1 compares the representative epigenetic patterns, cancer-specific contexts, and translational status across these settings.

DNA methylation illustrates why apparently similar epigenetic phenotypes should not be treated as equivalent across tumor types. In EBV-positive GC, extensive CpG island hypermethylation occurs in a virus-associated gastric epithelial context, whereas MLH1-associated methylation is more characteristic of the MSI GC subtype. CRC CIMP is instead commonly associated with the serrated pathway, BRAF mutation, proximal tumor location, MLH1 methylation, and MSI[55,89,90]. CRC CIMP may overlap with features enriched in CMS1, but it is not equivalent to the transcriptome-based CMS classification[134]. Thus, widespread CpG island hypermethylation represents a shared molecular pattern whose biological origin and clinical interpretation remain tumor- and subtype-specific. Similarly, the prognostic significance of global or LINE-1 hypomethylation is context-dependent. LINE-1 hypomethylation has been associated with poor outcome after curative resection in ESCC and with adverse prognosis in selected GC and CRC

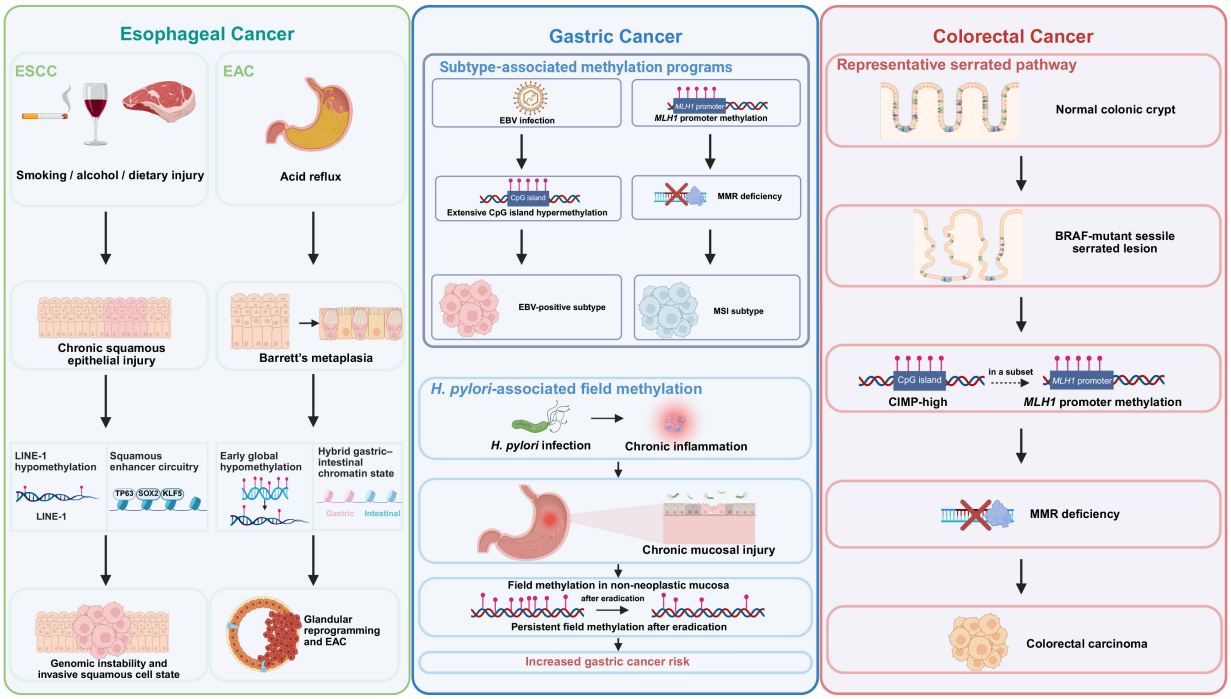

Figure 2. Tumor-specific epigenetic programs in gastrointestinal carcinogenesis. Representative epigenetic alterations are shown for ESCC, Barrett's-associated EAC, gastric cancer and the colorectal serrated pathway. These include LINE-1 or global hypomethylation, lineage-specific enhancer and chromatin states, EBV- and *Helicobacter pylori*-associated methylation, CIMP-high, MLH1 promoter methylation and mismatch-repair deficiency. Created in BioRender. ESCC: Esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; EBV: Epstein-Barr virus; MMR: DNA mismatch repair; CIMP:CpG island methylator phenotype.

cohorts[26,136,137]. However, there is no comprehensive analysis across distinct molecular subtypes and pathologic stages. Thus, its prevalence and prognostic impact may vary by tumor stage, molecular subtype, assay, and cohort composition. Also, LINE-1 hypomethylation is not a uniform feature of preneoplastic gastric lesions[138]. Therefore, its prognostic impact cannot be assumed to be consistent across the three cancers.

Notably, the greater volume of HDAC-related research in CRC should also be interpreted as an asymmetry in the evidence base rather than as evidence that HDAC dysregulation is intrinsically more important in CRC. The reviewed CRC literature includes extensive preclinical work on fluoropyrimidine resistance and selective HDAC inhibition. By contrast, ESCC studies remain concentrated on specific regulatory circuits. This imbalance reflects differences in model availability, historical drug-development priorities, and the larger CRC literature on chemotherapy resistance.

Translational development is also uneven. CRC currently has the clearest clinical applications, including multitarget stool DNA/FIT screening and *MLH1* promoter methylation testing. In Barrett's esophagus and EAC, non-endoscopic methylation testing has progressed from analytically validated laboratory-developed testing to clinical evaluation, but it is not established as routine biomarker testing. In GC, RIMS1 methylation is under prospective evaluation for risk stratification after *H. pylori* eradication. But it still requires implementation-level validation. Histone modifiers, chromatin-remodeling defects, ncRNAs, RNA editing, and m^{6}A regulators remain predominantly mechanistic, retrospective, or early-clinical-stage findings across the three cancers. Therefore, shared epigenetic mechanisms do not imply uniform biological or clinical effects, as their significance is shaped by lineage, etiological context, precursor state, molecular subtype, and the availability of clinically validated assays.

Table 1. Tumor-specific epigenetic patterns and translational status across esophageal, gastric, and colorectal cancers

Tumor type or subtype	Representative epigenetic alteration	Cancer-specific context	Translational status	References
ESCC	Promoter CpG island hypermethylation panels, including STK3- and ZNF418-containing regions	Squamous lineage; exposure-associated carcinogenesis; substantial inter- and intratumor methylation heterogeneity	Retrospective biomarker evidence	Pu *et al.*, 2017[32]; Talukdar *et al.*, 2021[23]
ESCC	Global DNA hypomethylation and LINE-1 methylation loss	Genomic instability associated with squamous carcinogenesis; prognostic effects vary by cohort and disease context	Retrospective biomarker evidence	Iwagami *et al.*, 2013[26]; Kawano *et al.*, 2014[24]
Barrett's esophagus/EAC	Early global hypomethylation and methylation-defined molecular patterns	Reflux-Barrett's-EAC sequence and glandular lineage reprogramming	Retrospective biomarker evidence	Alvarez *et al.*, 2011[45]; Jammula *et al.*, 2020[47]
EBV-positive and MSI gastric cancer	Subtype-associated CpG island hypermethylation and MLH1-associated methylation in MSI tumors	Virus- and mismatch-repair-associated molecular subtypes; distinct from CRC CIMP	Molecular classification	Cancer Genome Atlas Research Network, 2014[55]; Zouridis *et al.*, 2012[59]; Ajani *et al.*, 2025[87]
H. pylori-associated gastric cancer risk	Field methylation in non-neoplastic mucosa, including RIMS1 methylation	Persistent epimutation burden after inflammation-associated gastric injury and *H. pylori* eradication	Clinical validation	Maekita *et al.*, 2006[60]; Yamada *et al.*, 2025[61]
CRC, CIMP context	CIMP-associated promoter CpG island hypermethylation	Serrated pathway, BRAF mutation and MSI-associated tumor evolution; distinct from CMS classification	Molecular classification	Toyota *et al.*, 1999[89]; Ogino *et al.*, 2009[90]; Guinney *et al.*, 2015[134]
CRC, MLH1/PMS2-deficient tumors	MLH1 promoter methylation	Distinguishes many sporadic MLH1-deficient tumors from cases requiring further Lynch syndrome evaluation	Clinical implementation	Kuismanen *et al.*, 2000[13]; Aronson *et al.*, 2025[129]
CRC screening	Multitarget stool DNA methylation markers combined with fecal hemoglobin	Non-invasive screening in average-risk populations	Clinical implementation	Imperiale *et al.*, 2014[135]; Imperiale *et al.*, 2024[125]; Davidson *et al.*, 2021[126]
CRC screening, adults not completing recommended screening	Plasma methylated SEPT9	Blood-based screening for a defined average-risk population that has not completed other recommended screening	Clinical implementation	Jin *et al.*, 2015[127]; US Food and Drug Administration, 2016[128]
CRC blood-based screening	Combined cfDNA genomic and epigenomic signals, including methylation and fragmentation patterns	Average-risk population screening; performance differs between CRC and advanced precancerous lesions	Clinical implementation	Chung *et al.*, 2024[130]; US Food and Drug Administration, 2024[131]
CRC postoperative monitoring	ctDNA methylation markers and methylation haplotypes	Post-resection molecular monitoring and recurrence-risk assessment	Clinical validation	Symonds *et al.*, 2018[103]; Mo *et al.*, 2023[102]

ESCC: Esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; EBV: Epstein-Barr virus; MMR: DNA mismatch repair; MSI: microsatellite instability; CRC: colorectal cancer; CIMP: CpG island methylator phenotype; BRAF: B-Raf proto-oncogene; CMS: consensus molecular subtypes.

CONCLUSION

In summary, epigenetic dysregulation is a feature of and contributor to esophageal, gastric, and colorectal cancers. While aberrant DNA methylation yields the most clinically advanced biomarkers for early detection, prognosis, and treatment response across all three tumor types, implementation differs markedly by tumor type, and robust evidence remains limited for many proposed markers. However, the relative contribution of histone modifiers, chromatin remodelers, and RNA-mediated mechanisms varies by tumor subtype and anatomical context.

Looking forward, several priorities emerge in this field. First, functional dissection of epigenetic crosstalk within specific genetic backgrounds (e.g., *KRAS*-mutant CRC, EBV-positive gastric cancer) is necessary to identify context-dependent vulnerabilities. Second, single-cell multi-omic technologies will facilitate tracking

epigenetic heterogeneity during therapy resistance and metastasis. Third, prospective validation of multi-omic epigenetic panels in large, well-annotated cohorts is urgently required. This is particularly important because many epigenetic alterations are dynamic and may also arise in inflamed, aging, or premalignant tissues, making it difficult to distinguish true cancer-specific signals from background epigenetic remodeling or field effects.

For clinical translation, blood- or stool-based assays that capture dynamic DNA methylation changes have potential for integration into screening programs and minimal residual disease monitoring, but proposed roles in the population still require indication-specific prospective validation. Moreover, epigenetic drugs [HDAC inhibitors, DNA methyltransferase (DNMT) inhibitors, and emerging m^{6}A modulators] should be evaluated in rationally designed combination trials guided by tumor subtype and resistance mechanisms. Ultimately, incorporating epigenetic biomarkers into routine clinical workflows would enable precision risk stratification and real-time monitoring of treatment response across gastrointestinal cancers.

DECLARATIONS

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Authors' contributions

Designed the project and drafted the manuscript: Huang Z, Ma R
Drafted the manuscript: Xiao Z
Supervised and designed the study, acquired funding, and wrote the manuscript: Zhou X
All authors revised the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version 5.6-sol, released 2026-06-26) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflict of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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