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Review Article

Defective DNA Mismatch Repair as a Biomarker in Cancer Diagnosis and Immunotherapy: Review Article

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Abstract

The DNA mismatch repair (MMR) system is essential for maintaining genomic integrity by correcting base–base mismatches and insertion–deletion loops generated during DNA replication. Defects in this pathway result in microsatellite instability (MSI) and a hypermutated tumor phenotype with profound biological and clinical consequences. Over the past decade, deficient mismatch repair (dMMR) and MSI-high (MSI-H) status have emerged as robust biomarkers for cancer screening, molecular diagnosis, prognostic stratification, and prediction of response to immune checkpoint blockade (ICB). This narrative review summarizes the molecular biology of the MMR system, mechanisms leading to MMR deficiency, current diagnostic strategies for MSI/MMR assessment, and the pivotal role of dMMR as a predictive biomarker for immunotherapy across multiple cancer types. Emphasis is placed on clinical applications, limitations, and emerging directions in precision oncology.

Keywords: DNA mismatch repair; Microsatellite instability; dMMR; Immunotherapy; Lynch syndrome; colorectal cancer.

Introduction

The DNA mismatch repair (MMR) pathway represents one of the most essential genomic maintenance mechanisms in eukaryotic cells, safeguarding DNA fidelity during cell division. DNA replication is inherently prone to error due to the enormous length of the genome and the biochemical limitations of DNA polymerases. Although polymerases possess intrinsic proofreading activity, a significant proportion of mismatches and insertion–deletion loops escape correction at the replication fork. The MMR system acts as a post-replicative quality control mechanism, identifying and correcting these residual errors before they become permanently fixed mutations. Failure of this system leads to the accumulation of somatic mutations throughout the genome, with microsatellites being particularly vulnerable. Microsatellites are short, repetitive DNA sequences that are highly susceptible to polymerase slippage. In the absence of functional MMR, these sequences exhibit length variability, a phenomenon known as microsatellite instability (MSI). MSI is not merely a molecular footprint of repair deficiency but a driver of tumorigenesis through frameshift mutations in critical genes involved in cell cycle regulation, apoptosis, and DNA damage response. Clinically, dMMR/MSI-H tumors form a distinct molecular subgroup across multiple cancer types. In colorectal cancer, MSI-H tumors account for approximately 15% of early-stage cases but decline in frequency in metastatic disease, suggesting a unique biological behavior. Endometrial cancer exhibits one of the highest proportions of MSI-H tumors, reflecting the strong association between MMR deficiency and estrogen-driven carcinogenesis. Beyond these, MSI-H status has been

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documented in gastric, ovarian, small bowel, pancreatic, and urothelial carcinomas, reinforcing its pan-cancer relevance. The clinical significance of MMR deficiency was historically limited to prognostic stratification and identification of Lynch syndrome. However, this paradigm changed dramatically with the advent of immunotherapy. The tissue-agnostic approval of PD-1 inhibitors for MSI-H/dMMR tumors represented a watershed moment in oncology, establishing MMR deficiency as a predictive biomarker independent of tumor histology. This decision was grounded in the observation that MSI-H tumors harbor extraordinarily high tumor mutational burden, leading to abundant neoantigen formation and enhanced immune recognition. Importantly, MMR proteins are not isolated actors in genomic maintenance. They interact with base excision repair, nucleotide excision repair, and double-strand break repair pathways, thereby influencing cellular responses to both endogenous and exogenous DNA damage. These interactions explain the altered sensitivity of dMMR tumors to specific chemotherapeutic agents and environmental carcinogens [1] . Despite these advances, global implementation of MSI/MMR testing remains inconsistent, particularly in resource-limited settings, resulting in underutilization of life-altering therapies and missed opportunities for hereditary cancer detection [2].

The DNA Mismatch Repair System

Core MMR Proteins

The MMR system is a highly coordinated and evolutionarily conserved pathway that relies on the precise interaction of multiple protein complexes. Central to this system are the MutS and MutL homologs, which act sequentially to recognize DNA mismatches and initiate repair. The MutSα complex (MSH2–MSH6) is primarily responsible for detecting base–base mismatches and small insertion–deletion loops, which constitute the majority of replication errors. In contrast, MutSβ (MSH2–MSH3) specializes in recognizing larger insertion–deletion loops, particularly within repetitive DNA sequences. Following mismatch recognition, these MutS complexes recruit MutLα (MLH1–PMS2), which serves as a molecular scaffold coordinating downstream repair events. MutLα possesses endonuclease activity and orchestrates the recruitment of exonucleases that remove the error-containing DNA strand. DNA polymerase then resynthesizes the excised region, and DNA ligase seals the nick, restoring genomic integrity. A critical feature of the MMR system is the interdependence of its components. MLH1 is essential for the stability of PMS2, while MSH2 stabilizes both MSH6 and MSH3. Consequently, loss of one protein often results in secondary degradation of its binding partner. This biological principle underpins the diagnostic interpretation of immunohistochemistry, allowing pathologists to infer the underlying genetic defect based on staining patterns. Beyond their canonical repair functions, MMR proteins participate in signaling pathways that regulate apoptosis and cell cycle arrest in response to DNA damage. This broader role highlights why MMR deficiency confers not only genomic instability but also altered cellular responses to therapy, influencing both prognosis and treatment sensitivity.

Mechanisms of MMR Deficiency

Microsatellite Instability as a Diagnostic Biomarker

MMR deficiency can arise through several distinct molecular mechanisms, broadly categorized into hereditary and sporadic causes. Germline pathogenic variants in MLH1, MSH2, MSH6, PMS2, or EPCAM deletions define Lynch syndrome. These inherited defects confer a lifetime predisposition to multiple malignancies, often at a young age, with characteristic tumor spectra. In sporadic tumors, MMR deficiency most commonly results from epigenetic silencing rather than genetic mutation. MLH1 promoter hypermethylation is the predominant mechanism, particularly in colorectal cancer. This epigenetic alteration leads to transcriptional repression of MLH1, followed by secondary loss of PMS2. Such tumors are frequently associated with the CpG island methylator phenotype and activating BRAF mutations, distinguishing them from Lynch-associated cancers. Additional mechanisms include somatic biallelic mutations in MMR genes and post-translational modifications that impair protein stability or localization. Regardless of the initiating event, the functional consequence is a hypermutated genome characterized by abundant frameshift mutations and neoantigen generation. This hypermutated state forms the biological basis for the pronounced immunogenicity of dMMR tumors (3,4).

MSI Testing Modalities

The assessment of MSI/MMR status has evolved into a routine component of oncologic diagnostics, reflecting its profound therapeutic and hereditary implications. Immunohistochemistry (IHC) remains the most widely adopted initial screening tool due to its simplicity, rapid turnaround time, and ability to directly visualize protein expression within tumor cells. Loss of nuclear staining for one or more MMR proteins, in the presence of intact internal controls, strongly suggests dMMR. PCR-based MSI testing provides a complementary molecular approach

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by directly measuring length variations in microsatellite markers. Traditional panels classify tumors as MSI-H, MSI-low, or microsatellite stable based on the number of unstable loci. This method offers high analytical sensitivity but requires matched normal tissue, which may not always be available. Next-generation sequencing has introduced a more comprehensive approach, enabling MSI detection through bioinformatic analysis of insertion–deletion signatures across hundreds of loci. NGS platforms allow simultaneous evaluation of MSI status, tumor mutational burden, and actionable genomic alterations. However, interpretation requires careful validation, as discordance between IHC and molecular methods may occur due to tumor heterogeneity, low tumor cellularity, prior therapy, or atypical mutations with retained protein expression [6,7].

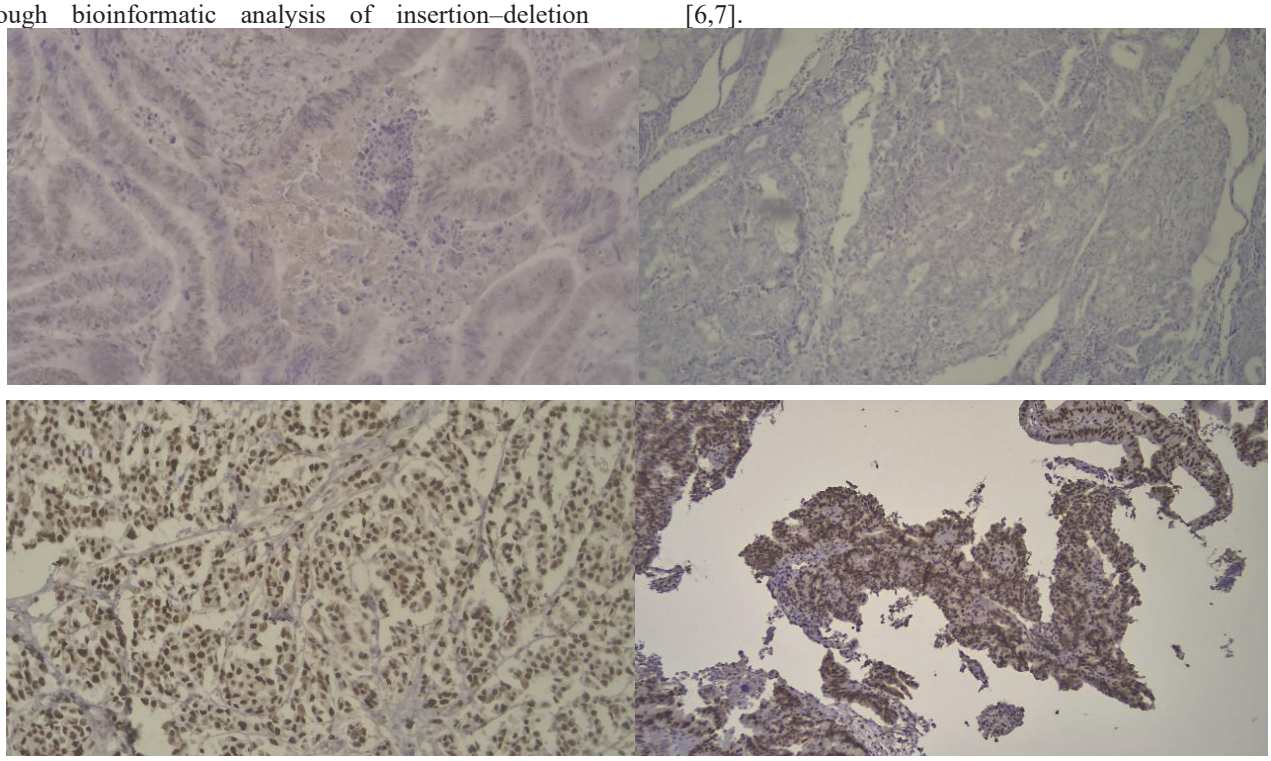

Figure 1: An illustration of various MMR and dMMR patterns in immunohistochemistry.

Clinical Indications for MSI Testing

Universal testing for microsatellite instability (MSI) or mismatch repair (MMR) deficiency has become a cornerstone of modern oncologic practice, reflecting the expanding clinical implications of this biomarker. Current international guidelines recommend universal MSI/MMR testing for all newly diagnosed colorectal and endometrial cancers, irrespective of patient age, tumor stage, or family history. This shift away from selective testing strategies is driven by the recognition that reliance on clinical criteria alone fails to identify a substantial proportion of patients with Lynch syndrome and underestimates the prevalence of sporadic dMMR tumors. In colorectal cancer, universal testing ensures accurate stratification of patients at diagnosis. MSI-H/dMMR tumors demonstrate distinct biological behavior, therapeutic responsiveness, and prognostic implications compared with pMMR/MSS tumors. From a therapeutic perspective, MSI status directly informs eligibility for immune checkpoint inhibitors, particularly in advanced or metastatic settings. Importantly, early identification of MSI-H status may influence treatment sequencing, avoidance of ineffective therapies, and enrollment in clinical trials evaluating immunotherapy in earlier disease stages. Endometrial cancer represents another paradigm where universal MSI/MMR testing has proven indispensable. A significant proportion of endometrial carcinomas exhibit MMR deficiency, often in the absence of a suggestive family

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history. Universal testing facilitates identification of Lynch syndrome–associated endometrial cancer, which may be the sentinel malignancy in affected women. Early detection enables targeted surveillance for colorectal and other associated cancers, thereby reducing long-term morbidity and mortality. Beyond colorectal and endometrial cancers, accumulating evidence supports expansion of MSI/MMR testing to additional tumor types. Gastric cancer, for example, includes a well-defined MSI-H molecular subtype characterized by favorable prognosis and heightened immunogenicity. Pancreatic, small bowel, biliary tract, prostate, and urothelial carcinomas also demonstrate clinically meaningful rates of MSI-H/dMMR, particularly in selected subgroups. As immunotherapy indications broaden, MSI/MMR testing is increasingly viewed as a pan-cancer diagnostic tool rather than a tumor-specific assay. Crucially, the clinical utility of MSI testing extends far beyond therapeutic decision-making. Identification of MSI-H/dMMR tumors serves as a critical gateway to hereditary cancer risk assessment. Tumors demonstrating loss of MMR protein expression or MSI-H status prompt further evaluation for Lynch syndrome through genetic counseling and germline testing. This process enables cascade screening of at-risk relatives, implementation of tailored surveillance protocols, and adoption of preventive strategies such as prophylactic surgery or intensified screening. From a public health perspective, universal MSI/MMR testing represents one of the most effective cancer prevention strategies currently available. Multiple studies have demonstrated that systematic tumor testing followed by germline evaluation substantially reduces cancer-related mortality at the population level. Moreover, the cost-effectiveness of universal testing has been consistently validated when long-term outcomes are considered. Collectively, these considerations firmly establish MSI/MMR testing as an essential component of contemporary oncologic care [9,17].

Prognostic Significance of dMMR

Mismatch repair deficiency exerts a profound yet context-dependent influence on tumor behavior, disease progression, and patient outcomes. Among solid tumors, colorectal cancer provides the most robust evidence regarding the prognostic implications of MSI-H/dMMR status. In early-stage disease, MSI-H colorectal cancers are consistently associated with favorable clinicopathologic features, including lower rates of lymphovascular invasion, reduced nodal involvement, and decreased propensity for distant metastasis. Numerous cohort studies and meta-analyses have demonstrated superior disease-free and overall survival in patients with stage II MSI-H colorectal cancer compared with their MSS counterparts.

The biological basis for this prognostic advantage is multifactorial. MSI-H tumors harbor exceptionally high tumor mutational burden, resulting in abundant neoantigen generation. These neoantigens elicit a strong antitumor immune response characterized by dense infiltration of cytotoxic T lymphocytes and activation of immune effector pathways. This immune surveillance not only limits tumor progression but may also enhance clearance of micrometastatic disease, contributing to improved outcomes. However, the prognostic impact of dMMR is not uniform across all cancer types or disease stages. In endometrial cancer, MSI-H status defines a molecular subgroup with heterogeneous outcomes. While some studies suggest improved survival compared with pMMR tumors, others report neutral or context-dependent effects influenced by histologic subtype, grade, hormonal environment, and immune microenvironment. For instance, MSI-H endometrioid carcinomas may demonstrate favorable outcomes, whereas high-grade tumors with complex immune escape mechanisms may not share this advantage. Gastric cancer provides another illustrative example. MSI-H gastric cancers often exhibit improved survival compared with MSS tumors, particularly in localized disease. These tumors tend to present at earlier stages, demonstrate reduced lymph node involvement, and exhibit strong immune activation. However, the prognostic benefit appears less pronounced in advanced-stage disease, where immune evasion mechanisms and tumor heterogeneity may attenuate the protective effect of MMR deficiency. Importantly, the prognostic significance of dMMR is also influenced by therapeutic context. In colorectal cancer, MSI-H status predicts lack of benefit from fluoropyrimidine monotherapy in the adjuvant setting, underscoring the necessity of integrating molecular biomarkers into treatment decision-making. These observations reinforce the concept that prognosis is not solely dictated by repair deficiency but arises from complex interactions between tumor genetics, immune contexture, and therapeutic interventions [4,14].

dMMR as a Predictive Biomarker for Immunotherapy

Biological Rationale

The remarkable sensitivity of dMMR tumors to immune checkpoint blockade represents one of the most compelling examples of biologically driven precision oncology. At the core of this phenomenon lies the hypermutated nature of dMMR tumors. Defective mismatch repair permits accumulation of thousands of somatic mutations,

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particularly frameshift mutations within coding microsatellites. These mutations generate novel peptide sequences that are recognized as non-self by the immune system. Neoantigen-rich tumors exhibit enhanced antigen presentation through major histocompatibility complex molecules, leading to robust activation of tumor-specific T cells. Consequently, dMMR tumors are characterized by dense infiltration of $CD8^+$ cytotoxic T lymphocytes, Th1-skewed immune responses, and upregulation of immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4. This state reflects adaptive immune resistance, wherein tumors evade immune destruction by engaging inhibitory pathways. Immune checkpoint inhibitors effectively reverse this immune suppression, unleashing pre-existing antitumor immune responses. Unlike pMMR tumors, which often lack sufficient neoantigen burden to initiate immune activation, dMMR tumors possess a primed immune microenvironment that is uniquely susceptible to checkpoint blockade. This biological framework explains the tissue-agnostic efficacy of immunotherapy in MSI-H/dMMR cancers [8] .

Clinical Evidence

The clinical efficacy of immune checkpoint inhibitors in MSI-H/dMMR tumors has been consistently demonstrated across multiple clinical trials and tumor types. Early phase studies revealed striking and durable responses in heavily pretreated patients, leading to accelerated regulatory approvals. Subsequent trials confirmed these findings, culminating in the first tissue-agnostic FDA approval of an anticancer therapy. In colorectal cancer, immunotherapy has fundamentally altered the treatment paradigm, particularly in metastatic disease. Trials such as KEYNOTE-177 established PD-1 inhibitors as superior to conventional chemotherapy in first-line treatment of MSI-H metastatic colorectal cancer. In endometrial cancer, integration of immunotherapy with chemotherapy in first-line regimens has significantly improved response rates and survival outcomes, redefining standards of care [3].

Resistance and Refinement of Biomarkers

Despite high response rates, a subset of dMMR tumors exhibits primary or acquired resistance to immunotherapy. Mechanisms of resistance are multifaceted and include defects in antigen presentation machinery, alterations in interferon signaling pathways such as JAK–STAT, immune exclusion mediated by stromal factors, and epigenetic reprogramming. Experimental studies have demonstrated that MLH1 loss activates innate immune signaling via the cGAS–STING pathway, enhancing antitumor immunity. Conversely, restoration of MLH1 expression or disruption of this pathway promotes immune evasion and therapeutic resistance [5]. These findings highlight the limitations of MSI/MMR status as a standalone biomarker and underscore the need for integrated predictive models incorporating genomic, epigenetic, and immune parameters [19].

Epigenetic Alterations and dMMR

Epigenetic dysregulation plays a central and multifaceted role in the pathogenesis of sporadic dMMR colorectal cancer, representing a critical molecular interface between inherited genomic stability mechanisms and environmentally influenced tumor evolution. Unlike genetic mutations, epigenetic alterations do not change the underlying DNA sequence but instead modulate gene expression through reversible chemical modifications of DNA and chromatin. These alterations are particularly relevant in colorectal carcinogenesis, where prolonged exposure to inflammatory stimuli, dietary factors, microbiome-derived metabolites, and aging-associated epigenetic drift converge to reshape the epigenomic landscape of colonic epithelial cells. Among epigenetic mechanisms, MLH1 promoter hypermethylation is the most extensively characterized and clinically significant event leading to mismatch repair deficiency in sporadic colorectal cancer. Hypermethylation of CpG islands within the MLH1 promoter region results in transcriptional silencing of the gene, abrogating MLH1 protein expression and causing secondary destabilization and loss of its binding partner PMS2. The functional consequence is complete disruption of the MutLα complex and subsequent failure of DNA mismatch repair, culminating in widespread microsatellite instability. This epigenetic inactivation of MLH1 accounts for the majority of sporadic MSI-H colorectal cancers and serves as a key molecular distinction from Lynch syndrome–associated tumors, which arise from germline mutations rather than epigenetic silencing [16,17]. MLH1 promoter hypermethylation is a defining hallmark of the CpG island methylator phenotype (CIMP), a distinct epigenomic subtype of colorectal cancer characterized by widespread hypermethylation across numerous gene promoters. Tumors exhibiting CIMP frequently harbor activating BRAF mutations, particularly the V600E variant, which further drives oncogenic signaling and reinforces epigenetic repression through activation of downstream MAPK pathways. The strong association between BRAF mutations, MLH1 hypermethylation, and MSI-H status provides a mechanistic framework linking oncogenic signaling,

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epigenetic remodeling, and genomic instability. Clinically, this association is exploited to differentiate sporadic dMMR tumors from Lynch syndrome–associated cancers, as the presence of BRAF mutations or MLH1 hypermethylation effectively excludes hereditary disease [5,10].Beyond DNA methylation, additional epigenetic mechanisms substantially contribute to tumor initiation, progression, and immune modulation in dMMR colorectal cancer. Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, play a pivotal role in regulating chromatin structure and gene accessibility. Aberrant patterns of histone modification can lead to transcriptional repression of tumor suppressor genes or inappropriate activation of oncogenic pathways. In the context of dMMR tumors, altered histone marks influence expression of genes involved not only in DNA repair and cell cycle regulation but also in antigen presentation, interferon signaling, and immune checkpoint regulation, thereby shaping the tumor immune microenvironment. MicroRNAs (miRNAs) represent an additional layer of epigenetic regulation with profound implications for tumor biology. Dysregulated miRNA expression in dMMR colorectal cancer affects key pathways governing cell proliferation, apoptosis, epithelial–mesenchymal transition, and immune evasion. Specific miRNAs have been implicated in modulating MMR gene expression, inflammatory signaling, and immune checkpoint molecule expression, thereby contributing to tumor heterogeneity and variability in therapeutic response [13,20]. Moreover, miRNA-mediated regulation is highly context-dependent, further complicating the biological behavior of dMMR tumors across different stages and microenvironmental conditions. Importantly, epigenetic alterations are inherently dynamic and potentially reversible, distinguishing them from fixed genetic mutations and rendering them attractive therapeutic targets. Pharmacologic agents targeting DNA methylation and histone-modifying enzymes have demonstrated the ability to reprogram tumor epigenomes, restore expression of silenced genes, and enhance tumor immunogenicity. In dMMR colorectal cancer, epigenetic therapies may augment immune recognition by increasing neoantigen expression, upregulating antigen presentation machinery, and modulating immune checkpoint pathways. These effects provide a strong biological rationale for combining epigenetic therapies with immune checkpoint inhibitors to overcome primary or acquired resistance. Integration of epigenetic profiling into routine clinical practice holds promise for refining risk stratification, improving prognostic assessment, and guiding therapeutic decision-making. Comprehensive epigenomic characterization may help distinguish biologically distinct subsets of MSI-H tumors, predict immunotherapy responsiveness, and identify patients who may benefit from epigenetic–immunotherapeutic combination strategies. As our understanding of the interplay between epigenetics, genomic instability, and tumor immunity continues to evolve, epigenetic dysregulation is increasingly recognized as a central driver of colorectal cancer pathogenesis and a critical target for next-generation precision oncology approaches [8,16].

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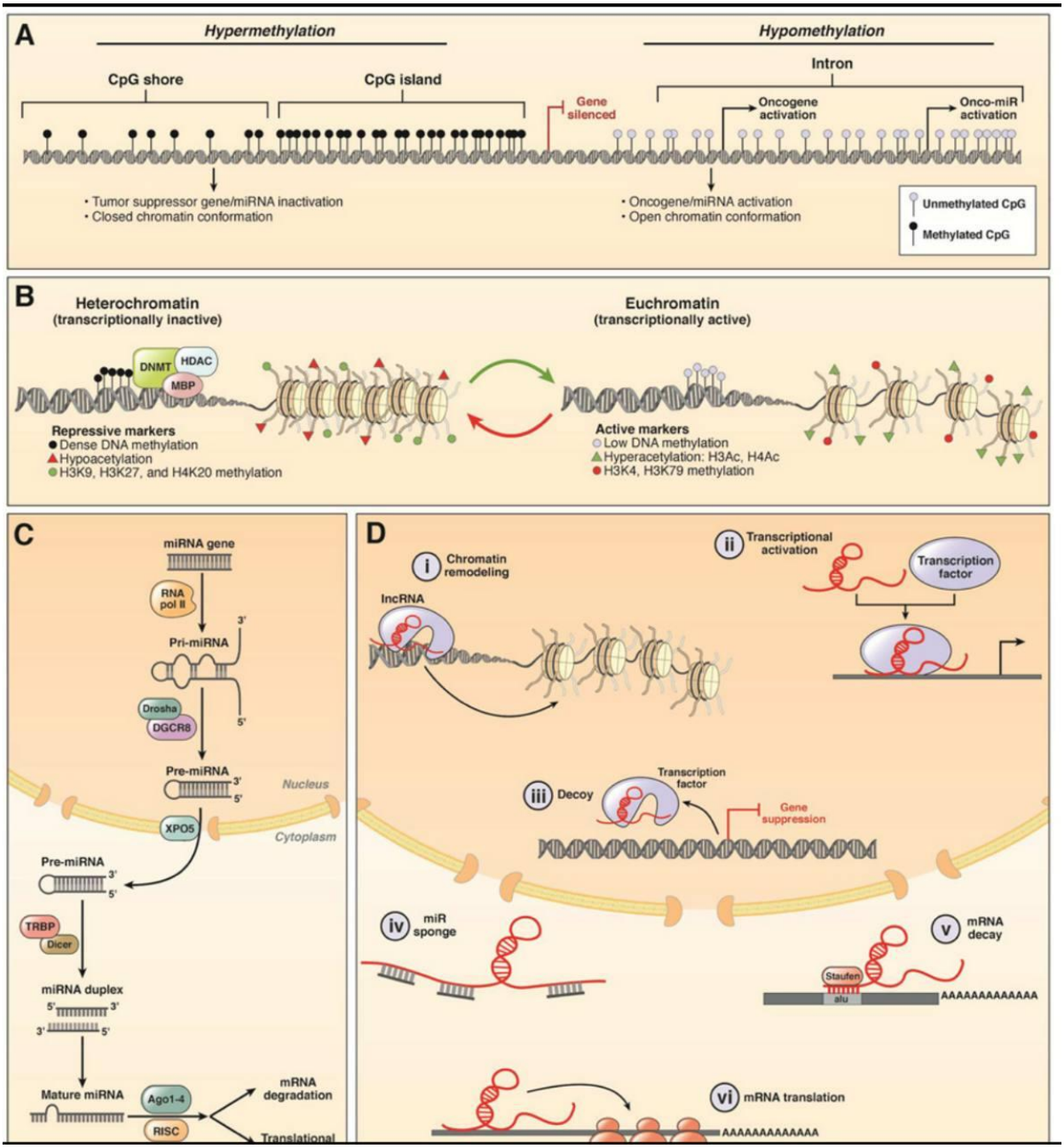

Figure 2: An illustration of various epigenetic alterations in colorectal cancer.(16)

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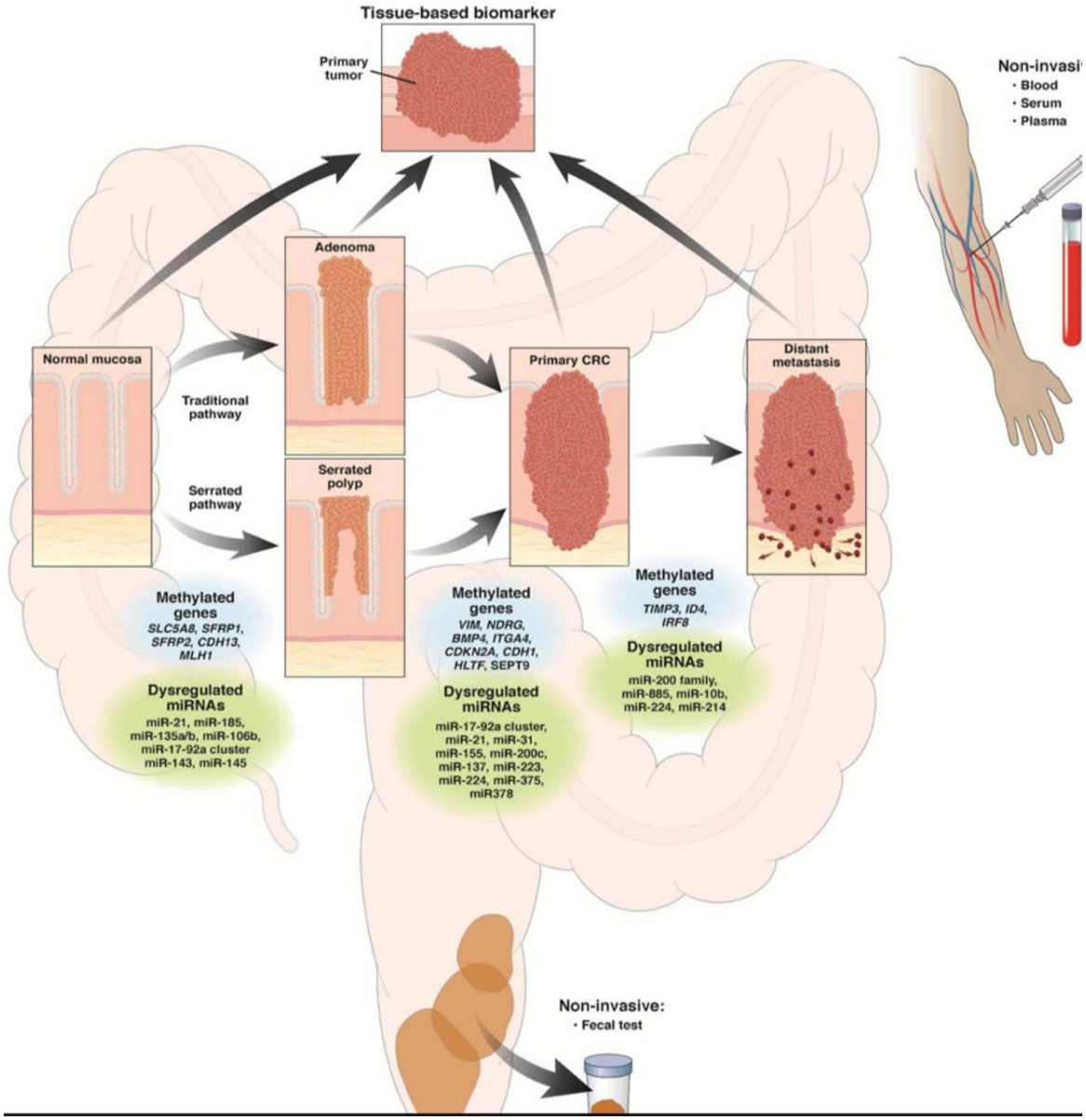

Figure 4: A schematic view of bench-to-bedside aspects of colorectal cancer epigenetics.(16)

Lynch Syndrome and Hereditary Implications

Lynch syndrome is the most common hereditary colorectal cancer syndrome and arises from germline pathogenic variants in MMR genes or EPCAM deletions. The syndrome is characterized by autosomal dominant inheritance, early-onset malignancies, and a broad tumor spectrum. Universal tumor testing has emerged as the most effective strategy for identifying affected individuals, outperforming traditional clinical criteria. Early identification of Lynch syndrome enables implementation of intensive surveillance protocols, risk-reducing interventions, and cascade testing of relatives. These measures have been shown to dramatically reduce cancer incidence and mortality, underscoring the profound clinical and public health impact of systematic MSI/MMR testing [17].

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Future Perspectives

dvances in sequencing technologies, liquid biopsy, artificial intelligence–assisted diagnostics, and combination immunotherapeutic strategies are poised to further expand the clinical utility of MSI/MMR testing. Overcoming resistance mechanisms in both dMMR and pMMR tumors remains a central research priority, with the ultimate goal of refining precision oncology and improving patient outcomes [19].

Conclusion

Defective DNA mismatch repair and microsatellite instability–high (MSI-H) status have become central pillars in modern cancer diagnostics and therapeutic stratification. Their clinical relevance extends beyond tumor classification to encompass hereditary cancer risk assessment, prognostic evaluation, and prediction of response to immunotherapy. Routine integration of MSI/MMR testing into oncologic practice has significantly improved identification of patients with Lynch syndrome and enabled timely implementation of surveillance and preventive strategies. From a therapeutic perspective, recognition of dMMR/MSI-H tumors has reshaped treatment paradigms across multiple malignancies, most notably through the adoption of immune checkpoint inhibitors in a tissue-agnostic manner. These advances underscore the importance of understanding tumor biology at the molecular and immunologic levels and highlight the success of precision oncology approaches driven by robust biomarkers.

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