J. Adv. Med. Pharm. Biomed. Res.; **(2026),** Volume 2, Issue 3, 217-225

Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research

Journal homepage: https://www.jampbr.com

DOI: 10.22034/jampbr.2026.576925.1089

The Role of Mismatch Repair Deficiency (MMR) in Endometrial Carcinoma Subtyping: A Pathologic Review

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Article info

Received: 21.11.2025

Accepted: 26.02.2026

Available Online: 27.02.2026

Checked for Plagiarism: Yes

Keywords:

Mismatch Repair Deficiency, Molecular Subtyping, MSI-High, Immunotherapy Prediction

ABSTRACT

Assessing Mismatch Repair MMR status via immunohistochemical loss of MLH1 and PMS2 proteins is paramount in endometrial carcinoma EC. This deficiency, indicative of a hypermutable phenotype, serves as a critical prognostic factor and, more significantly, a strong predictive biomarker for therapeutic response, particularly guiding the successful application of immune checkpoint blockade therapies in patients with advanced or recurrent disease. This narrative review synthesized literature on MMR deficiency in Endometrial Carcinoma using systematic searches (PubMed, Scopus, etc.) up to January 2026. Key terms focused on MMR status, molecular subtyping, and immunotherapy in EC. Inclusion required peer-reviewed studies addressing pathological assessment or molecular classification with direct clinical correlation, ensuring a robust foundation for synthesis. MMR deficiency dictates the therapeutic strategy in Endometrial Carcinoma due to the resulting high Tumor Mutational Burden, which generates abundant neoantigens and creates "hot" tumors. This genomic instability confers exquisite sensitivity to Immune Checkpoint Inhibitors (ICBs), leading to tumor-agnostic FDA approval for anti-PD-1 therapy in MSI-H cancers. Therefore, MMR status functions primarily as a predictive biomarker, guiding access to highly effective immunotherapy, especially in advanced or recurrent disease settings, superseding its complex prognostic implications.

Introduction

Endometrial carcinoma EC stands as the most frequently diagnosed gynecologic malignancy in developed nations, primarily affecting postmenopausal women. Historically, the management and prognostic stratification of EC relied heavily on morphological features, primarily the degree of myometrium invasion, tumor grade, and histological subtype, as codified by the International Federation of Gynecology and Obstetrics FIGO staging system (1). While this paradigm has served as the bedrock of clinical practice for decades, it frequently fails to delineate prognostic ally distinct groups, leading to therapeutic heterogeneity and suboptimal personalized treatment strategies (2). The realization that EC is not a singular disease entity but rather a heterogeneous spectrum of molecularly diverse conditions has catalyzed a profound shift toward molecular classification, an evolution critical for precision oncology. Central to this molecular revolution is the identification and characterization of tumors exhibiting defects in the Mismatch Repair MMR pathway (3).

The Mismatch Repair system is a highly conserved DNA repair mechanism responsible for recognizing and correcting errors such as base-base mismatches and insertion/deletion loops that arise during DNA replication (4). This meticulous surveillance is crucial for maintaining genomic fidelity; failure of this system results in a hyper mutable state, leading to the accumulation of somatic mutations at an accelerated rate. When MMR components are rendered non-functional, these cancers are classified as Mismatch Repair Deficient Mimed (5). In the context of sporadic cancers, this deficiency most

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frequently arises from the epigenetic silencing via promoter hyper methylation of the MLH1 gene, although mutations in other key MMR genes like MSH2, MSH6, or PMS2 can also be implicated, particularly in hereditary syndromes such as Lynch Syndrome HNPCC (6).

The prevalence of MMR deficiency in EC is substantial, accounting for approximately 20-30% of all cases, depending on the cohort studied and the diagnostic methodology employed. This high prevalence underscores its clinical significance, positioning MMR status as a key determinant in disease behavior, prognosis, and responsiveness to systemic therapies. Pathologically, the diagnostic determination of MMR status is typically performed using immunohistochemistry IHC staining for the four core MMR proteins: MLH1, MSH2, MSH6, and PMS2(7). The loss of expression of one or both MLH1/PMS2 proteins, or MSH2/MSH6 proteins, is the direct immunohistochemically surrogate for MMR deficiency. The pattern of loss is critical: loss of MLH1 is often associated with sporadic cases driven by MLH1 methylation, whereas concurrent loss of MSH2 and MSH6 often points towards an underlying germline MSH2 mutation or Lynch Syndrome (8). Proper interpretation of these IHC profiles is paramount, as it dictates the subsequent necessity for germline testing to screen at-risk family members. Furthermore, the microscopic evaluation of the tumor microenvironment in MMRd tumors frequently reveals a prominent tumor-infiltrating lymphocyte TIL burden. This dense inflammatory infiltrate is a direct consequence of the high mutational load generating numerous neoantigens, which the immune system recognizes as foreign (9).

The prognostic significance of MMR deficiency in EC is complex and context-dependent, heavily interwoven with histological subtype. In the context of Type, I endometrioid carcinomas, particularly the low-grade variants, the presence of MMR deficiency often associated with the p53 wild-type status is generally linked to a favorable prognosis when compared to their MMR-proficient counterparts, especially in early-stage disease (10). However, when MMR deficiency coexists with the p53 abnormal status, which is more characteristic of high-grade, Type II tumors, the prognostic implication shifts, often signaling a more aggressive phenotype. This divergence highlights why traditional histological grading alone is insufficient; the integration of molecular features like MMR status provides necessary stratification beyond just morphology (11).

Perhaps the most transformative clinical implication of identifying MMRd EC relates to therapeutic susceptibility. The hyper mutated state that characterizes MMRd tumors renders them profoundly sensitive to immune checkpoint blockade ICB therapies. Because of the massive production of neoantigens resulting from high MSI, these tumors exhibit a higher degree of immunogenicity than MMR-proficient tumors (12). This has positioned MMRd status, and by extension, high MSI, as a key predictive biomarker for response to agents targeting the PD-1/PD-L1 axis. The U.S. Food and Drug Administration FDA has approved ICB therapy for any unrespectable or recurrent solid tumor that exhibits MSI-High, which is synonymous with absent MMR protein expression, irrespective of the primary tumor site. For endometrial carcinoma, this classification has opened a critical therapeutic avenue, particularly for patients with advanced or recurrent disease where standard chemotherapy options offer limited long-term benefit (13).

Therefore, this review aims to synthesize the current understanding of MMR deficiency within the broader landscape of endometrial carcinoma subtyping. We will meticulously examine the pathological nuances of interpreting MMR protein loss via IHC, distinguishing between sporadic and hereditary mechanisms. Furthermore, we will explore the established relationships between MMR status and the prevailing molecular classifications, particularly in relation to the four established EC subtypes POLE-mutated, MSI/MMRd, Copy Number High/p53-abnormal, and Copy Number Low/p53-wildtype. By integrating these pathological findings with contemporary molecular insights, this review intends to underscore the indispensable role of MMR assessment as a cornerstone for accurate prognostication, risk stratification, and, most importantly, the strategic deployment of modern, immune-based systemic therapies in the evolving management paradigm of endometrial cancer. The transition from purely morphological assessment to an integrated clinic pathologic framework is not merely an advancement but a necessity to optimize outcomes for our patients.

Material and methods

This investigation was structured as a comprehensive narrative review designed to synthesize the current literature concerning the role of Mismatch Repair Deficiency MMR in the molecular subtyping, prognostication, and therapeutic stratification of endometrial carcinoma EC. The literature search was systematically executed across major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, to capture the breadth of published research. The search was unrestricted by publication date, encompassing all articles available up to the beginning of January 2026, with a mandatory inclusion criterion that all retrieved articles be published in the English language. Key search terms employed individually and in combination via Boolean operators included:

"Mismatch Repair Deficiency," "MMR," "Endometrial Carcinoma," "Endometrial Cancer," "MLH1," "PMS2," "MSH2," "MSH6," "Microsatellite Instability," "MSI," "Pathology," "Molecular Subtyping," and "Immunotherapy." Inclusion criteria for the final selection mandated that the studies must: (1) directly address the pathological assessment or molecular classification of EC related to MMR status; (2) provide primary data, comprehensive review, or consensus guidelines; and (3) be peer-reviewed publications or official clinical society recommendations. Studies were systematically excluded if they focused exclusively on non-endometrial malignancies, addressed only Lynch Syndrome prevalence unrelated to EC carcinogenesis, or were limited to animal or in vitro models without clinical correlation. The selection process involved an initial title and abstract screening, followed by a full-text review by the authors to confirm adherence to these established eligibility criteria, thereby ensuring the final synthesis reflects the most relevant and impactful contributions to this field.

Results

Endometrial Cancer: From Histopathology to Molecular Subtyping

Endometrial cancer (EC) stands as the most common gynecologic malignancy in developed nations, profoundly impacting global public health, particularly due to its high incidence, which continues to rise, often correlating with increasing rates of obesity and metabolic syndrome. While EC is frequently diagnosed at an early stage, resulting in a generally favorable prognosis compared to many other solid tumors, the high overall burden of disease both in terms of new cases and mortality from recurrence or advanced stages underscores its clinical significance (14). The traditional reliance on the clinic pathological classification system, predominantly encapsulated by the International Federation of Gynecology and Obstetrics (FIGO) staging and the purely histological grading (e.g., Grade 1, 2, or 3 based on glandular architecture and nuclear atypia), has served as the initial cornerstone for management decisions. However, these systems exhibit significant limitations in predicting recurrence risk and guiding systemic therapy, leading to clinical dilemmas. For instance, patients classified within the same FIGO stage or histological grade often display starkly divergent clinical courses; low-grade tumors can recur aggressively, while some higher-grade lesions may behave indolently. This inherent biological heterogeneity strongly implied that the morphological features alone were insufficient to capture the underlying molecular drivers responsible for tumor progression and therapeutic response, signaling an urgent need for a more precise, biologically informed stratification system (figure1) (15).

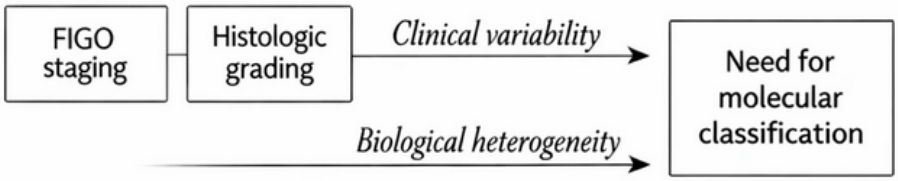

Figure 1. Summarizing limitations of traditional endometrial cancer (EC)

The imperative to refine prognostication and personalize treatment strategies catalyzed the transition toward molecular classification, powerfully demonstrated by The Cancer Genome Atlas (TCGA) consortium. The TCGA research identified four distinct molecular subgroups of EC, revolutionizing the understanding of this heterogeneous disease: P53-aberrant (often high-grade serous-like), Copy-number-high (characterized by frequent high-level copy number alterations), Microsatellite Instability (MSI), and POLE-ultra mutated (16). This framework moves beyond architectural appearance to classify tumors based on actionable genomic features, fundamentally reshaping prognostic stratification and treatment eligibility. Crucially integrated within this molecular landscape is the status of the Mismatch Repair (MMR) system. Defects in MMR, which lead to a hyper mutable phenotype characterized by numerous frameshift mutations in microsatellites (the MSI-high group), are central to this new paradigm. MMR deficiency, whether due to germline mutations (Lynch syndrome) or somatic epigenetic silencing, identifies a large subset of ECs that not only share distinct histological features but, more importantly, are exquisitely sensitive to immunotherapy. Thus, defining the MMR/MSI status is no longer an ancillary pathological feature but a primary, actionable component of the modern molecular classification, guiding clinicians toward targeted therapeutic avenues and away from less effective conventional chemotherapy regimens for this specific molecular subset (17).

The Mismatch Repair System and DNA Fidelity

The fidelity of the genome is paramount for cellular survival and organismal health, a standard upheld by intricate DNA repair pathways that meticulously

correct errors introduced during replication. Among the most critical of these mechanisms is the Mismatch Repair (MMR) system, a post-replicative quality control apparatus designed to recognize and excise errors, primarily base-base mismatches and insertion/deletion loops (IDLs) arising from polymerase slippage, that escape the proofreading activity of DNA polymerases. The functional integrity of MMR is orchestrated by a conserved network of proteins that operate in a highly coordinated manner (18). The core functional complexes are heterodimers formed between the MutS homolog (MSH) and MutL homolog (MLH) families. Specifically, the recognition machinery is primarily driven by the MSH2/MSH6 heterodimer (MutSα\alphaα) which exhibits high affinity for single base-pair mismatches, and the MSH2/MSH3 heterodimer (MutSβ\betaβ) which specializes in larger IDLs (19). Once a mismatch is recognized and bound, the signal is transduced to the downstream effector proteins, comprising the MutL homologs. The primary downstream complex responsible for initiating repair excision involves MLH1 coupled with PMS2 (MutLα\alphaα), which partners with the recognized mismatch site. This MutLα\alphaα complex facilitates the recruitment of downstream factors, including PCNA and exonuclease 1 (EXO1), ultimately leading to the excision of the newly synthesized, erroneous DNA strand segment extending from the mismatch, followed by resynthesis by DNA polymerase δ\deltaδ and ligation (20).

The sequential action of these protein components recognition (MSH2/MSH6 or MSH2/MSH3), signaling and recruitment (MLH1/PMS2), and subsequent excision/resynthesis ensures that the error rate in the human genome is suppressed by several orders of magnitude. When any critical component of this cascade is functionally lost, the consequences for genomic stability are profound, leading directly to a state known as hyper mutability. In the context of cancer, particularly Endometrial Cancer (EC), the inactivation of MMR components most frequently through promoter hyper methylation of MLH1 or inactivating mutations in any of the core genes results in the accumulation of thousands of novel somatic mutations across the genome (21).

This overwhelming mutational burden manifests visibly at specific, highly repetitive sequences scattered throughout the genome known as microsatellites (short tandem repeats). In a functional MMR context, these regions are constantly monitored, and replication slippage errors are corrected. However, in the absence of functional MMR, these slippage events persist and accumulate, leading to measurable changes in the length of the microsatellite tracts between the tumor tissue and normal adjacent tissue (22). This phenomenon is precisely defined as Microsatellite Instability (MSI). Tumors exhibiting a high frequency of these length alterations are termed MSI-High (MSI-H). The MSI-H phenotype is not merely a marker of defective DNA repair; it represents a specific, highly immunogenic molecular subtype of EC. The inactivation of MMR leads to a massive influx of frameshift mutations within coding regions, frequently targeting genes that encode crucial regulatory proteins, most notably microsatellite-containing sequences within tumor suppressor genes or genes involved in immune evasion (23). Critically, the resultant high tumor mutational burden generates a large quantity of novel, non-self-peptides displayed on the cell surface as neoantigens, making the MSI-H tumor highly visible to the host immune system and explaining their characteristic and dramatic responsiveness to immune checkpoint blockade therapies (24).

Pathological Detection of MMR Deficiency

The accurate pathological identification of Mismatch Repair (MMR) deficiency is the critical gateway to classifying Endometrial Cancer (EC) into the prognostic ally and therapeutically relevant MSI-High molecular subgroup. While molecular testing, specifically microsatellite instability (MSI) testing, remains the definitive gold standard for functional assessment, the initial and often most informative tool employed in the routine diagnostic setting is Immunohistochemistry (IHC). IHC evaluates the nuclear expression status of the key MMR proteins: MLH1, PMS2, MSH2, and MSH6(25). A normal, proficient MMR phenotype is characterized by strong, diffuse nuclear staining for all four proteins in both tumor cells and background internal control (e.g., stromal or lymphoid cells). Conversely, deficiency is marked by the complete absence (loss of expression) of one or more of these proteins in the tumor nuclei, while internal control cells retain expression. The specific pattern of protein loss is pivotal for distinguishing between sporadic and inherited causes (26). The concurrent loss of both MLH1 and PMS2 staining typically indicates that the pathway has been disrupted downstream, most commonly due to the epigenetic silencing via methylation of the MLH1 promoter in sporadic tumors, a mechanism highly prevalent in older patients and higher-grade ECs. In contrast, the loss of expression of MSH2 and/or MSH6 often suggests a germline defect affecting one of the upstream recognition components, pointing toward Lynch Syndrome, an inherited predisposition syndrome, making this pattern a crucial red flag for genetic counseling referral (27).

The interpretation of MMR protein loss patterns must always be integrated within the broader histopathological context of the tumor. MMR-deficient (MMRd) tumors frequently exhibit distinct morphological features that can alert the pathologist to request further testing, even when the clinical

suspicion for Lynch Syndrome is low (28). These morphological correlates often include a prominent tumor-infiltrating lymphoid component (TILs), a mucinous or micro papillary architecture, or a general appearance of high-grade dedifferentiation, though it must be noted that MMR deficiency can occur across various histological types. Therefore, the visual examination of the tumor morphology, guided by the four-protein IHC panel, serves as an essential correlative step, framing the molecular investigation (29) (figure 2).

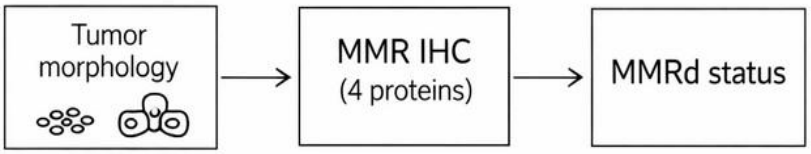

Figure 2. Relationship between tumor morphology and MMR deficiency assessment in cancer pathology

While IHC provides rapid mechanistic insight into which protein is absent, it is an assessment of protein presence, not necessarily function. Consequently, confirmatory testing is mandatory for definitive classification and to establish the etiology. Confirmation of functional deficiency is achieved through molecular testing, typically by assessing the degree of microsatellite instability (MSI) using a panel of repetitive sequences (30). A high degree of instability (MSI-H) confirms the functional consequence of the observed protein loss, validating the tumor's hyper mutable status. Furthermore, when the IHC pattern suggests a sporadic cause (i.e., MLH1/PMS2 loss), further testing for MLH1 promoter methylation is performed (31). Detection of methylation definitively confirms a sporadic origin, indicating that the tumor developed independently of a germline mutation. Conversely, an IHC loss pattern suggestive of Lynch Syndrome (MSH2/MSH6 loss) necessitates germline sequencing to identify the pathogenic constitutional mutation, thereby securing the patient's diagnosis and enabling cascade screening for at-risk relatives. This multi-tiered pathological and molecular diagnostic workflow is essential for accurate patient stratification in modern EC management (32).

MMR Status in Molecular Subtyping of Endometrial Carcinoma

The advent of comprehensive molecular profiling, exemplified by The Cancer Genome Atlas (TCGA) initiative, fundamentally transformed the understanding of Endometrial Carcinoma (EC) from a purely histopathologic entity into a biologically heterogeneous disease. This classification delineated four distinct molecular subgroups POLE-Mutated, Copy-Number High (p53-Abnormal), Copy-Number Low, and the MMR-Deficient/Microsatellite Instability-High (MMRd/MSI-H) group each possessing unique genomic drivers, clinic pathologic features, and distinct prognostic trajectories (33). The recognition of MMR deficiency as an independent molecular entity underscores its critical role as a primary determinant of EC pathogenesis and clinical outcome, moving beyond its function simply as a prognostic marker (34).

The MMRd/MSI-H subgroup is characterized by a profound functional deficiency in DNA mismatch repair, leading to widespread hyper mutation. Clinically and histologically, these tumors often present with features that can overlap with traditional low-grade Type I ECs, such as endometriosis histology and high levels of mismatch repair protein loss via IHC, yet they exhibit a biological aggressiveness that warrants their distinct molecular placement (35). A hallmark of these tumors is a significant infiltration of the tumor microenvironment by immune cells, evidenced by a high density of Tumor-Infiltrating Lymphocytes (TILs). This immunological 'hot' state is a direct consequence of the high tumor mutational burden (TMB) generating numerous neoantigens, which forms the mechanistic basis for their remarkable sensitivity to immune checkpoint inhibitor therapies. Furthermore, within the TCGA framework, the MMRd group generally correlates with tumors exhibiting wild-type p53 status, distinguishing them sharply from the Copy-Number High group, which is defined by widespread genomic instability and concurrent p53 aberration (36).

Distinguishing the MMRd/MSI-H group from the other TCGA categories is crucial for therapeutic stratification. The POLE-Mutated subgroup, characterized by ultra-mutation driven by pathogenic mutations in the POLE exonuclease domain, shares a high TMB with MMRd tumors but lacks MMR deficiency and p53 alterations, often presenting with an extremely favorable prognosis (37). In contrast, the Copy-Number High group is defined by extensive chromosomal alterations and is inextricably linked to p53 mutations, leading to a highly aggressive clinical course and resistance to standard therapies. The Copy-Number Low group represents tumors with few genomic alterations, often correlating with the classical Type I endometriosis carcinomas. Therefore, the MMRd/MSI-H status effectively partitions a large cohort of Ecs those driven by defects in DNA maintenance rather than widespread copy number changes or polymerase proofreading errors into a distinct biological entity defined by immune recognition (38). This framework dictates that while

morphology may suggest low grade, the underlying MMR deficiency mandates aggressive molecular testing, as the resulting MSI-H status dictates therapeutic access to novel immunotherapies, irrespective of traditional grading schema limitations (39) (figure 4).

Clinical Significance and Prognostic Implications

The prognostic implications of Mismatch Repair Deficiency (MMRd) in Endometrial Carcinoma (EC) represent a complex duality, shifting from a traditionally favorable indicator in early-stage disease to a crucial predictive biomarker in advanced or recurrent settings. In localized, surgically treated EC, particularly within the endometriosis histology often associated with the MMRd molecular subgroup, the presence of MSI-High status has historically suggested a less aggressive clinical course, often correlating with lower tumor grade and earlier stage presentation (40). This apparent advantage is frequently attributed to the biological profile associated with MMRd, which often excludes the high genomic chaos seen in p53-aberrant, copy-number high tumors. However, this perception of universal clinical benefit is complicated by studies involving later-stage disease or recurrence, where the inherent high mutational burden may eventually drive clonal evolution towards more aggressive phenotypes, challenging the notion of MMRd as an exclusively benign prognostic factor across all clinical scenarios (41) (figure 3).

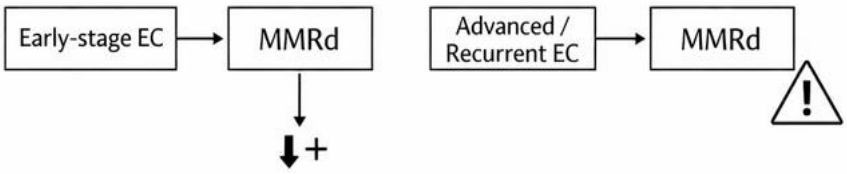

Figure 3. Dual prognostic role of MMR deficiency in endometrial cancer

This inherent ambiguity mandates a critical re-framing of MMR status in contemporary oncology: its primary value may not be as an independent, monolithic prognostic determinant, but rather as a powerful predictive biomarker for treatment response. The most significant clinical impact of identifying an MMRd/MSI-H tumor lies in its near-universal predictive relationship with efficacy of immune checkpoint inhibitors (ICIs) (42). As previously established, the hyper mutated state inherent to MMR deficiency generates a high density of neoantigens, leading to a profoundly inflamed tumor microenvironment rich in Tumor-Infiltrating Lymphocytes (TILs). This characteristic immunological signature dictates that these tumors are highly vulnerable to agents targeting the PD-1/PD-L1 axis (43).

Consequently, when MMR deficiency is identified, the focus of clinical interpretation must pivot toward therapeutic decision-making. In the context of early-stage EC, while the survival difference between MMRd and proficient tumors may narrow or disappear after standard-of-care surgery, the identification of MMRd serves as a critical stratification tool for adjuvant therapy decisions. For patients with high-risk features or recurrence, confirming an MMRd/MSI-H status provides robust evidence to pursue systemic immunotherapy, often leading to durable responses in patients who might otherwise fail conventional platinum-based chemotherapy or hormonal therapy alone. This shift highlights the evolution of cancer diagnostics: a molecular finding that once served primarily to describe tumor biology now dictates the therapeutic pathway. Therefore, MMR status is best understood not as a simple measure of favorable versus unfavorable outcome on its own, but as the strongest known predictor of response to immunotherapy across the spectrum of EC presentation (44).

Therapeutic Implications: Predictive Biomarker for Immunotherapy

The heightened sensitivity of Mismatch Repair Deficient (MMRd) tumors to Immune Checkpoint Inhibitors (ICBs) is mechanistically rooted in their underlying genomic instability. The functional loss of MMR pathways prevents the accurate repair of errors introduced during DNA replication, resulting in a dramatically increased Tumor Mutational Burden (TMB) (45). This hyper mutability translates directly into the production of a large number of aberrant, non-self-proteins known as neoantigens. The abundance of these neoantigens effectively flags the cancer cells as foreign to the host immune system, leading to a robust and sustained adaptive immune response characterized by a dense infiltration of cytotoxic T-lymphocytes, classifying these tumors as “immunologically hot.” (46)

This strong immunological signature has led to unprecedented regulatory action. Based on compelling evidence demonstrating high response rates across various tumor types sharing this feature, the U.S. Food and Drug Administration (FDA) granted a tumor-agnostic approval for ICB therapy specifically targeting PD-1/PD-L1 pathways for any solid tumor exhibiting Microsatellite Instability-High (MSI-H) or confirmed MMRd status, regardless of the cancer’s primary site of origin. This marked a significant paradigm shift, prioritizing the molecular mechanism over the organ of origin (47).

For Endometrial Carcinoma, this translates directly into standard-of-care guidelines for advanced or recurrent disease. Landmark clinical trials, such as KEYNOTE-158, demonstrated substantial objective response rates and durable clinical benefit when treating patients with previously treated, advanced MSI-H/MMRd EC with pembrolizumab. Consequently, ICB therapy has rapidly secured a definitive role in the management of advanced or recurrent EC, often utilized in the first-line setting in combination with chemotherapy (e.g., carboplatin/paclitaxel) or as subsequent monotherapy for progression after initial treatment. The current clinical position mandates that all recurrent or metastatic EC patients undergo universal molecular testing, with a positive MMRd/MSI-H result immediately qualifying them for evaluation for ICB-based regimens, underscoring its role as the foremost predictive biomarker in this disease context (48).

Discussion

The systematic assessment of Mismatch Repair (MMR) status is no longer a supplementary diagnostic step but rather a central, non-negotiable component of modern Endometrial Carcinoma (EC) pathology. Integrating immunohistochemically evaluation of MMR proteins with molecular sequencing protocols moves beyond mere subtyping; it functions as a critical decision-making matrix that directly informs personalized therapeutic strategies (49). By accurately placing a tumor within the TCGA framework, MMR assessment immediately distinguishes those cancers driven by a failure in DNA fidelity, thereby dictating eligibility for highly effective immune checkpoint blockade. This molecular delineation ensures that patients benefit from treatments uniquely tailored to their tumor's biological vulnerability, optimizing response rates and potentially mitigating unnecessary exposure to less effective conventional systemic therapies that lack a targeted molecular rationale for this subgroup (50).

Looking forward, the research trajectory confirms that the utility of MMR assessment is poised for further expansion beyond its current established role in predicting immunotherapy response. Future investigations are heavily focused on understanding how MMR deficiency interacts with other treatment modalities. This includes elucidating whether the MMRd phenotype confers differential sensitivity or resistance to standard chemotherapy backbones, such as platinum-based agents, which are known to induce DNA damage (51). Furthermore, understanding the underlying genomic landscape of MMRd tumors will be paramount in designing rational combination therapies perhaps pairing ICBs with novel targeted agents or optimizing sequencing strategies to maximize the durable remission achieved in this clinically distinct patient population. Thus, the continued centrality of MMR assessment remains foundational for advancing precision oncology in EC (52).

Conclusion

In summation, the assessment of Mismatch Repair (MMR) status transcends basic molecular subtyping to serve as the pivot point for precision oncology in Endometrial Carcinoma, acting as the primary predictive biomarker for guiding immunotherapy selection based on high Tumor Mutational Burden and resultant immunogenicity. Future investigations must continue to refine this framework by elucidating MMR's role in resistance/sensitivity to conventional chemotherapy and informing next-generation combination regimens, thereby cementing its enduring importance as a foundational determinant of personalized therapeutic strategy for this heterogeneous malignancy.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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