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REVIEW

Microsatellite Instability in Colorectal Cancer: Rethinking the Roles of Age and Family History

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Abstract

Background: Microsatellite instability (MSI) is a hallmark of defective DNA mismatch repair (MMR) and a well-established molecular subtype of colorectal cancer (CRC). MSI testing has gained increasing clinical relevance in the diagnosis of Lynch syndrome (hereditary nonpolyposis colorectal cancer) and in guiding treatment strategies. **Objective:** This review explores the diagnostic and prognostic implications of MSI in CRC, with a particular emphasis on the role of patient age and family history in identifying high-risk individuals. **Methods:** We reviewed the current literature on MSI, Lynch syndrome, and familial CRC, including data on molecular mechanisms, screening tools (MSI testing, IHC, predictive models), and epidemiological trends in both hereditary and sporadic CRC cases. **Results:** MSI-High (MSI-H) status is strongly associated with Lynch syndrome in early-onset CRC cases (<50 years) and in those with positive family history. However, a substantial proportion of MSI-H tumors occur sporadically in older adults (>60 years) without known familial risk, often due to MLH1 promoter hypermethylation. Family history-based screening demonstrates limited sensitivity, missing up to 60% of MSI-H cases. Universal MSI testing improves identification of both hereditary and sporadic cases and is now widely recommended. Moreover, MSI-H tumors show favorable prognosis and are predictive of better response to immunotherapy. **Conclusion:** While age and family history remain important in assessing CRC risk, they are insufficient as standalone criteria for Lynch syndrome screening. Universal MSI testing offers a more reliable approach for early diagnosis, risk stratification, and treatment planning in colorectal cancer. Further research is needed to refine predictive models and integrate MSI testing into broader population screening protocols.

Keywords: Microsatellite instability- colorectal cancer- Lynch syndrome- family history- age- mismatch repair

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1. Introduction

Colorectal cancer (CRC) is a major global health burden and ranks among the top causes of cancer-related morbidity and mortality [1-3]. While most CRC cases are sporadic, approximately 3–7% are hereditary, with Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) being the most common inherited form [4, 5]. Lynch syndrome arises from germline mutations in DNA mismatch repair (MMR) genes, leading to microsatellite instability (MSI), a defining molecular signature of this condition [6, 7].

The MMR system normally safeguards genomic integrity by correcting base mismatches during DNA replication. When inactivated, typically through mutations in key genes such as MLH1, MSH2, MSH6, and PMS2, DNA errors accumulate, resulting in MSI [4]. Tumors with high MSI (MSI-H) exhibit expansion or contraction of microsatellite regions and are strongly associated with Lynch syndrome. However, MSI is not exclusive to hereditary CRC: up to 15% of sporadic CRCs also show MSI-H, often due to somatic inactivation of MLH1 via promoter hypermethylation and BRAF mutations [5-7].

Given the clinical implications of MSI in diagnosis, prognosis, and treatment, especially its predictive value for immunotherapy response, understanding the role of

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age and family history in MSI-related CRC has become essential. This review aims to explore the diagnostic and prognostic significance of MSI, with particular focus on its association with patient age and familial cancer history, and to evaluate current evidence supporting universal MSI testing in clinical practice.

2. Clinical and Molecular Approaches for Identifying Lynch Syndrome Risk

2.1 Traditional Clinical Criteria: Amsterdam and Bethesda Guidelines

Lynch syndrome was historically recognized based on family clustering of colorectal and other associated cancers. The Amsterdam I criteria were the first formal tool developed to identify individuals likely carrying MMR gene mutations [8, 9]. These criteria focused on early-onset colorectal cancer (CRC) and required three affected family members across two generations, with at least one diagnosed before age 50. The Amsterdam II criteria later expanded to include extracolonic Lynch-associated tumors, such as endometrial and small bowel cancers.

Despite their specificity (~98%), the sensitivity of Amsterdam criteria remains low (~22%), which limits their effectiveness as a standalone screening tool [10-13]. To improve case detection, the Bethesda Guidelines were developed, incorporating broader clinical and pathological factors. The revised Bethesda criteria, which include features such as early age at diagnosis and tumor histology (e.g., mucinous type or presence of tumor-infiltrating lymphocytes), offer higher sensitivity (~82%) but still miss a substantial number of Lynch syndrome cases [10-13].

2.2 Quantitative Risk Models: MMR predict, MMR pro, PREMM

In response to the limitations of rigid clinical criteria, several statistical models have been developed to estimate the probability of an underlying MMR gene mutation using clinical and familial data.

MMR predict [14]:

- Designed for newly diagnosed CRC patients.
- Includes variables such as sex, age at diagnosis, tumor location (proximal vs. distal), and personal/family history of CRC or endometrial cancer.
- In a validation cohort, achieved sensitivity of 94% and specificity of 91%.

MMR pro [15]:

- Uses detailed personal and family history, including results of prior MSI or IHC testing.
- Covers MLH1, MSH2, and MSH6 mutations.
- Can also estimate cancer risk for unaffected relatives.
- Demonstrated better predictive power than Bethesda guidelines.

PREMM1,2,6 [16-17]:

- Estimates mutation risk in MLH1, MSH2, and MSH6 based on personal and family cancer history.
- Highest sensitivity (90%) but lower specificity (67%).
- Online tools make it accessible in clinical practice.
- Does not incorporate tumor test results directly, but these can complement the risk estimate.

2.3 Tumor-Based Testing: MSI and IHC

The integration of molecular pathology has dramatically improved the detection of Lynch syndrome in CRC patients.

MSI Testing:

MSI testing detects genomic instability by comparing repeat sequences in tumor and normal tissue using PCR or NGS. Tumors are classified as:

- MSI-High (MSI-H): instability in ≥30% of loci.
- MSI-Low (MSI-L): instability in <30%.
- Microsatellite Stable (MSS): no instability [18-22].

Immunohistochemistry (IHC):

IHC testing evaluates the expression of MMR proteins (MLH1, MSH2, MSH6, PMS2) in tumor tissue [23]. Loss of specific protein expression suggests the corresponding gene may be mutated or epigenetically silenced. For example, isolated loss of MSH2 indicates a likely germline mutation, while loss of MLH1/PMS2 may result from MLH1 promoter hypermethylation (suggesting sporadic origin) [23-25]. When MSI-H or abnormal IHC results are found, germline genetic testing is recommended to confirm Lynch syndrome and inform family risk [25].

2.4 Comparative Performance and Recommendations

Universal MSI/MMR testing is recommended for all newly diagnosed CRC cases to improve detection of mismatch repair deficient tumors.

Clinical criteria and prediction models provide useful frameworks for Lynch syndrome risk assessment, but they are limited by their dependence on accurate family history and subjective clinical judgment (Table 1). In contrast, molecular testing particularly MSI and IHC offers objective and highly sensitive strategies for detecting mismatch repair deficiency. Universal testing strategies that combine tumor-based and clinical approaches now represent the gold standard in Lynch syndrome

Table 1. Comparative Performance of Clinical Prediction Models for Lynch Syndrome

Approach	Sensitivity	Specificity	Requires Family History	Comments
Amsterdam Criteria	~22%	~98%	Yes	Very strict; low detection rate [28].
Revised Bethesda	~82%	~77%	Yes	Broader, but still misses cases [26].
MMRpredict	~94%	~91%	Partially	Strong clinical tool [29].
MMRpro	High	High	Yes	Includes tumor data [29].
PREMM1,2,6	~90%	~67%	Yes	Easy to use; lower specificity [17].
MSI/IHC Testing	~95%	~90%	No	Direct molecular evidence [30].

Table 2. Comparison of Familial (Lynch Syndrome) vs. Sporadic MSI Colorectal Cancer

Category	Familial CRC (Lynch Syndrome)	Sporadic MSI CRC
Cause of MSI	Germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2)	Somatic hypermethylation of MLH1 promoter (epigenetic silencing)
Inheritance	Autosomal dominant (hereditary)	Not inherited (acquired)
MSI-H Frequency	>90% of Lynch CRCs are MSI-H	10–20% of sporadic CRCs are MSI-H
Age at Diagnosis	Typically <50 years	Usually >60 years
Tumor Location	More commonly left-sided or rectal	Predominantly right-sided (proximal colon)
Family History	Strong family history of CRC and related cancers	Usually absent
Gender Distribution	No strong gender bias	Slight female predominance (esp. in right-sided tumors)
MMR Protein Loss	MSH2, MSH6, PMS2 loss common; MLH1 also possible	MLH1 loss predominant (via hypermethylation)
BRAF Mutation	Rare	Frequently present (indicative of sporadic origin)
Extent of MSI	Less extensive MSI	More extensive MSI across markers
Clonal Heterogeneity	Lower heterogeneity	Higher heterogeneity (affects immune response)
Prognosis	Generally favorable; germline testing advised	Good prognosis; may respond well to immunotherapy
Clinical Implications	Germline testing for patient and relatives recommended	BRAF mutation and MLH1 methylation testing to exclude Lynch syndrome

identification [19, 26, 27]. Diagnostic Accuracy and Utility of MSI-Related Prediction Models.

3. MSI and Family History

3.1 Role of MSI in Lynch Syndrome

Microsatellite instability (MSI) is a hallmark of defective DNA mismatch repair (MMR) and plays a central role in the pathogenesis of Lynch syndrome, the most common inherited form of colorectal cancer (CRC) [31]. Germline mutations in MLH1, MSH2, MSH6, or PMS2 impair the MMR system, allowing replication errors to accumulate in microsatellite regions, resulting in MSI. More than 90% of Lynch-associated CRCs exhibit MSI-high (MSI-H) status [31, 32].

MSI testing has become a standard initial screening tool to identify patients at risk for Lynch syndrome. Common testing methods include the Bethesda panel and the pentaplex panel, which categorize tumors as MSI-H (instability in ≥2 markers), MSI-low (instability in 1 marker), or microsatellite stable (MSS) [33, 34]. However, MSI testing alone is not diagnostic. Confirmation requires additional analyses such as immunohistochemical (IHC) staining for MMR proteins and germline genetic testing [33-35].

3.2 Familial vs. Sporadic MSI-H CRC

MSI is not exclusive to Lynch syndrome. Approximately 15–20% of all CRCs with MSI-H arise from inherited causes, while the remaining 80–85% is sporadic [36-37]. Sporadic MSI-H tumors typically result from somatic hypermethylation of the MLH1 promoter and are frequently associated with BRAF mutations and CpG island methylator phenotype (CIMP) [38]. These tumors occur more often in older adults and show distinct clinicopathological features compared to Lynch-related tumors [39]. The table below (Table 2) summarizes key differences between familial and sporadic MSI-H colorectal cancers [40-44].

3.3 Correlation between MSI-H and Family History

Although MSI-H status is statistically associated with a positive family history, this correlation is weaker than often assumed. Studies have shown that the sensitivity of family history in detecting MSI-H CRC ranges from 36.5% to 77%, with specificity ranging from 25% to 77.5% [44, 45]. For example, a large German study found that while MSI-H was more common in patients with family history (27.1% vs. 16.5%), most MSI-H cases actually occurred in those without such history [44, 46].

This discrepancy highlights a key clinical challenge: relying solely on family history for Lynch syndrome screening leads to underdiagnosis. Indeed, up to 60–65% of MSI-H tumors may be missed if family history is the only criterion used [44, 45].

Moreover, regional and ethnic differences influence this relationship. In some Asian populations, the prevalence of MSI-H CRC can exceed 40%, with stronger family history associations, whereas Western populations generally show lower MSI-H prevalence (15–20%) and weaker familial links [47, 48]. Genetic background, reporting accuracy, and cultural factors likely contribute to these differences [47, 49].

3.4 Clinical Implications and Recommendations

Given the limited sensitivity of family history–based screening, current guidelines recommend universal MSI testing for all newly diagnosed CRC patients [41, 42]. While family history may complement risk assessment alongside factors such as young age, tumor location, histological features, and molecular testing, most MSI-H tumors arise sporadically [43-52]. These findings underscore the central role of universal MSI testing in accurate risk stratification and clinical management of colorectal cancer.

4. MSI and Patient Age

4.1. Prevalence and Molecular Characteristics of MSI-High Tumors in Early-Onset Colorectal Cancer

Early-onset colorectal cancer (EOCRC) is generally

defined as CRC diagnosed before the age of 50 years, although varying age cutoffs (e.g., <40 or <45 years) have been used across studies, contributing to heterogeneity in reported MSI-H prevalence among EOCRC cohorts. Microsatellite instability-high (MSI-H) tumors are significantly more prevalent among EOCRC patients compared to older individuals. These tumors in younger patients frequently exhibit high tumor mutational burden (TMB) and distinctive molecular signatures, highlighting a unique biological profile [53].

Epidemiological studies report that the prevalence of MSI-H among EOCRC patients ranges from 19.7% to 41%, depending on the age threshold (e.g., ≤45 or ≤40 years) and population studied [49]. A pooled odds ratio (OR) of ~1.34 (95% CI: 1.24–1.45) confirms a higher likelihood of MSI-H status in early-onset versus late-onset CRC. Even after excluding hereditary syndromes such as Lynch syndrome, MSI remains modestly more common in EOCRC, suggesting a potential link to sporadic mechanisms [55].

Histologically, MSI-H tumors in younger patients are often located in the right colon and associated with mucinous differentiation. Importantly, these tumors also demonstrate better overall prognosis compared to microsatellite-stable (MSS) tumors [56]. In contrast, the prevalence of MSI-H declines markedly with age, with only about 10% of CRC patients aged 71–80 years displaying MSI-H status [57].

4.2. Diagnostic and Therapeutic Implications of MSI-H in Early-Onset CRC

MSI-H tumors possess a hypermutated phenotype that leads to a robust anti-tumor immune response. MSI status is a key biomarker for diagnosing Lynch syndrome and predicting response to immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 inhibitors [54, 55].

In EOCRC, MSI-H tumors often lack BRAF mutations unlike their sporadic late-onset counterparts and are enriched in proximal colon tumors. These features further support the distinct biology of EOCRC with MSI-H [56].

Although Lynch syndrome is more common in EOCRC, MSI-H remains independently associated with younger age, even in non-hereditary cases, suggesting a broader etiological role [61].

4.3. MSI as a Biomarker: Screening and Limitations in Young Populations

Currently, MSI testing is primarily employed for tumor characterization and identifying individuals with Lynch syndrome, particularly those with a suggestive personal or family history [59].

Despite its value, MSI testing is not recommended as a population-wide screening tool in young individuals due to limited sensitivity and cost-effectiveness. Only 10–15% of CRCs are MSI-H, and this rate is even lower in EOCRC. Nevertheless, identifying MSI-H status remains critical for guiding targeted therapies and identifying high-risk individuals [57, 58].

4.4. Epidemiological Trends and the Role of MSI in Early-Onset CRC

Global trends show a rising incidence of EOCRC, especially in high-income countries, linked to changing lifestyle factors (e.g., obesity, Western diets) and improved surveillance [59]. Males are more frequently affected, and regional disparities are evident in East Asia, North America, and Oceania.

From a molecular perspective, MSI-H tumors are disproportionately represented in EOCRC, often driven by inherited syndromes like Lynch syndrome. These tumors are associated with favorable prognosis, distinct pathology (e.g., mucinous features), and strong immunogenicity making MSI a key biomarker for prognosis and therapy selection [57].

5. Discussion

Microsatellite instability plays a central role in the pathogenesis and classification of CRC, with distinct implications based on age and hereditary background. Our review highlights that MSI-H tumors are significantly more prevalent among EOCRC cases, even after excluding hereditary syndromes like Lynch syndrome [33, 60]. This suggests a potential role for sporadic MSI in young patients, often associated with right-sided location, mucinous features, and better prognosis.

Family history, while important, is not always a reliable predictor of MSI or Lynch syndrome, as many cases occur without meeting clinical criteria. This supports current guidelines recommending universal MSI or mismatch repair (MMR) testing in all CRC cases [34, 46].

In older patients, sporadic MSI-H tumors are commonly driven by MLH1 promoter hypermethylation and BRAF mutations, and differ molecularly and clinically from Lynch-associated tumors [38].

Therapeutically, MSI-H status predicts excellent response to immune checkpoint inhibitors such as pembrolizumab and nivolumab, particularly in metastatic settings [61, 62]. This reinforces MSI as both a diagnostic and predictive biomarker.

Although early age at diagnosis and a positive family history remain important clinical indicators for Lynch syndrome, our review highlights their limited sensitivity when used in isolation. A substantial proportion of MSI-H colorectal cancers particularly in early-onset CRC occur in patients without a strong familial background. These findings strongly support universal MSI/MMR testing as the standard of care, with age and family history serving as complementary rather than decisive factors in clinical decision-making.

In summary, MSI testing should be considered not only for hereditary cancer screening but also for prognostic and therapeutic decisions, especially in younger patients who may otherwise go unrecognized without a family history.

In conclusion, while patient age and family history contribute valuable contextual information in colorectal cancer risk assessment, they are insufficient as standalone criteria for identifying MSI-H tumors or Lynch syndrome. Universal MSI/MMR testing provides a more sensitive

and equitable approach, particularly in early-onset colorectal cancer, where MSI-H tumors may arise even in the absence of a strong family history. Integrating molecular testing with clinical parameters enables more accurate diagnosis, optimized surveillance, and personalized therapeutic strategies.

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