MSInsight

Series 1

Understanding Microsatellite Instability : Insights and Implications

A Four-Part Series by MSInsight

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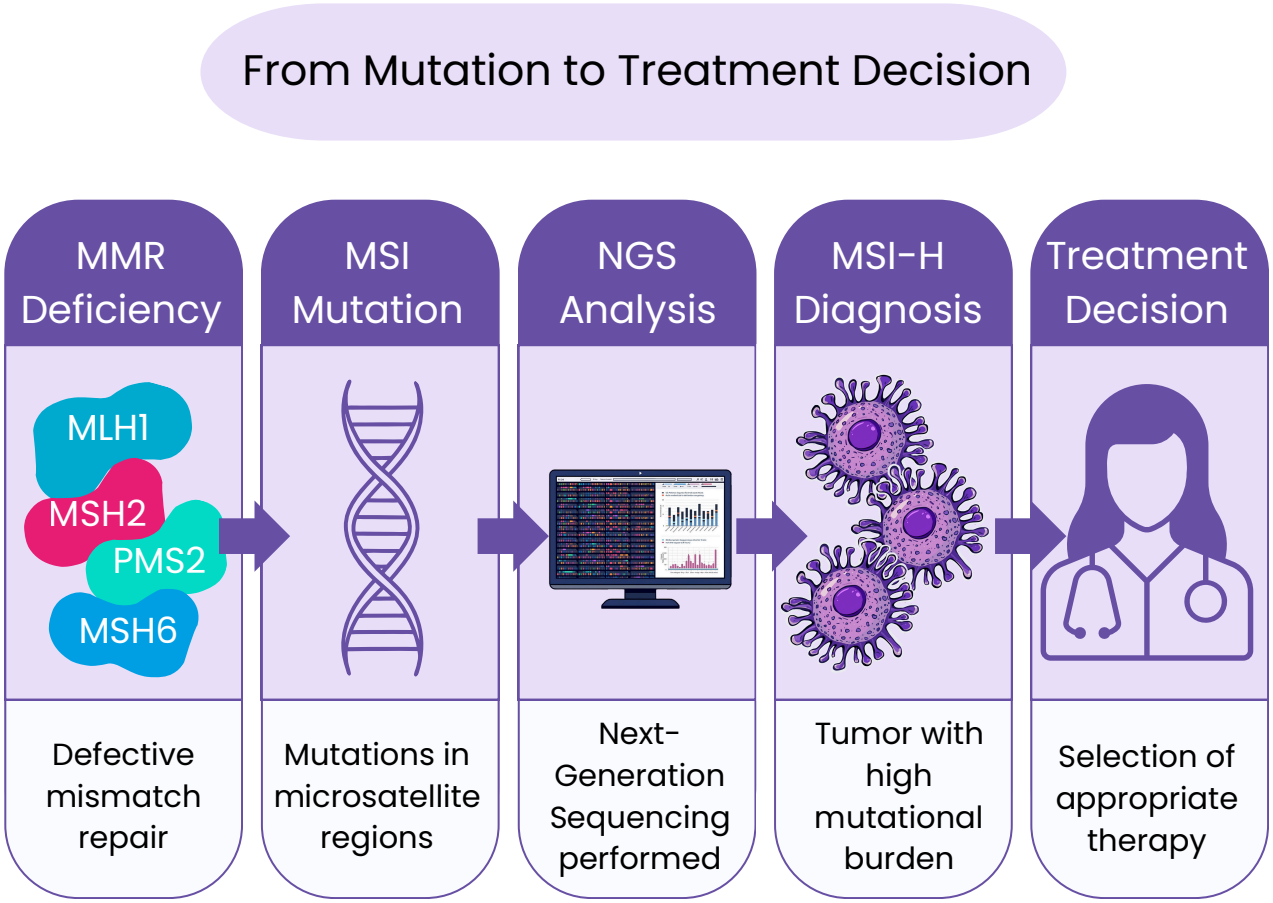
Background

Microsatellite instability (MSI) has become a central biomarker in cancer biology, driven by defects in the DNA mismatch repair system that lead to increased genomic instability and a high mutational burden. This molecular signature influences tumor development, immune recognition, and therapeutic response, particularly to immunotherapy, making MSI essential to modern precision-oncology strategies.

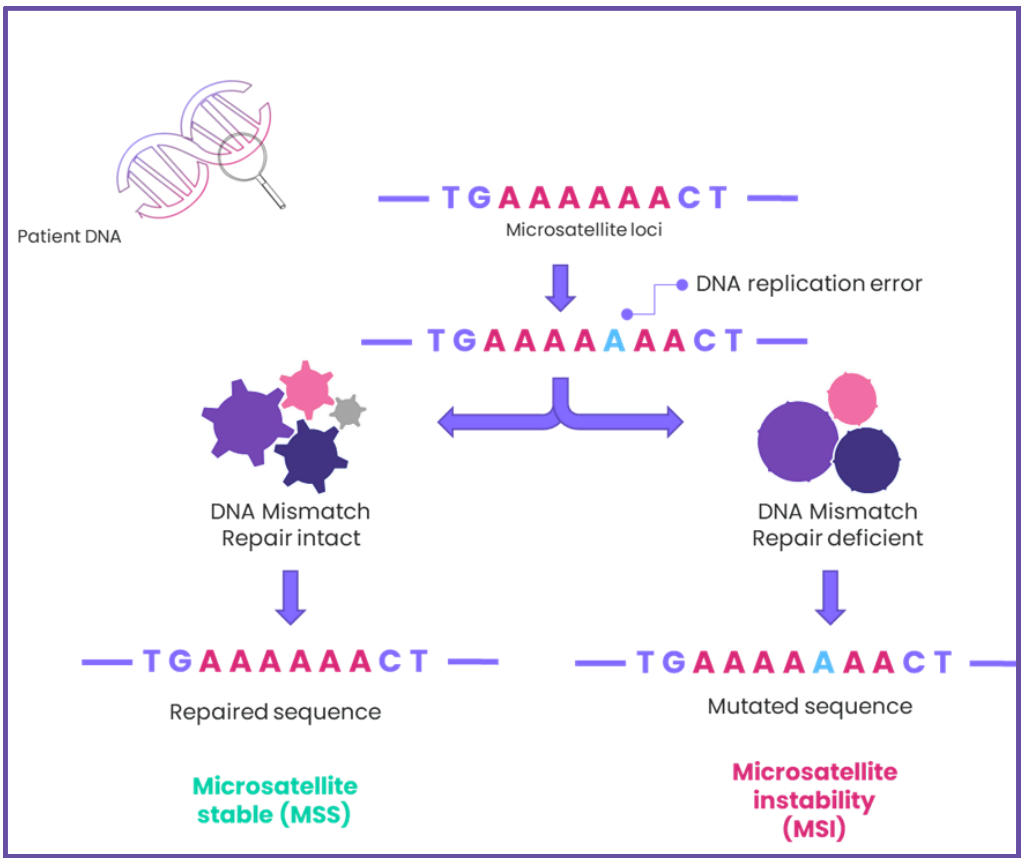
This white paper is the first in a four-part educational series on MSI. In this installment, we introduce the fundamental biology of MSI, explain the mechanisms underlying mismatch-repair deficiency, and outline the clinical relevance of MSI across tumor types. The following papers will build on this foundation by examining current diagnostic approaches, therapeutic decision-making, and hereditary forms of MSI — ultimately setting the stage for discussion of emerging strategies and advanced analytical tools in the field.



Understanding the Complexity of MSI

Microsatellite Instability (MSI) is a phenomenon characterized by the accumulation of insertion and deletion mutations in microsatellite regions of the genome due to defects in the DNA mismatch repair (MMR) system.

These microsatellites, which are short, repetitive DNA sequences, become unstable when the MMR mechanism fails to correct replication errors.
MSI is observed in a vast majority of cancer type, especially in solid tumors, making it a key biomarker for both prognosis and treatment selection.



The presence of MSI is particularly significant in cancers associated with Lynch syndrome, an inherited disorder caused by germline mutations in the MMR genes. Tumors exhibiting MSI often demonstrate increased responsiveness to immunotherapy due to their high tumor mutational burden (TMB), which generates neoantigens capable of eliciting an anti-tumor immune response. Understanding the molecular basis of MSI is crucial for optimizing targeted therapies and improving patient outcomes.

MSI status results from a deficiency in the DNA mismatch repair (MMR) system. This phenomenon is common in colorectal, endometrial, and gastric cancers, where MSI-H tumors can comprise 10–30% of cases depending on location and stage. Lynch syndrome, caused by germline mutations in MMR genes, contributes to around 15% of all MSI-H cases, while the rest are predominantly sporadic and associated with somatic hypermethylation of MLH1. (Hause et al., 2016)

MSI is also detected in a wide range of cancer types, with a frequency rate between 1% to 5% (including pancreatic, glioblastoma, kidney, esophageal, small intestine, biliary tract…). Even if it can be considered rare, **it is worth testing for.**

MSI Prevalence in Different Cancer Types

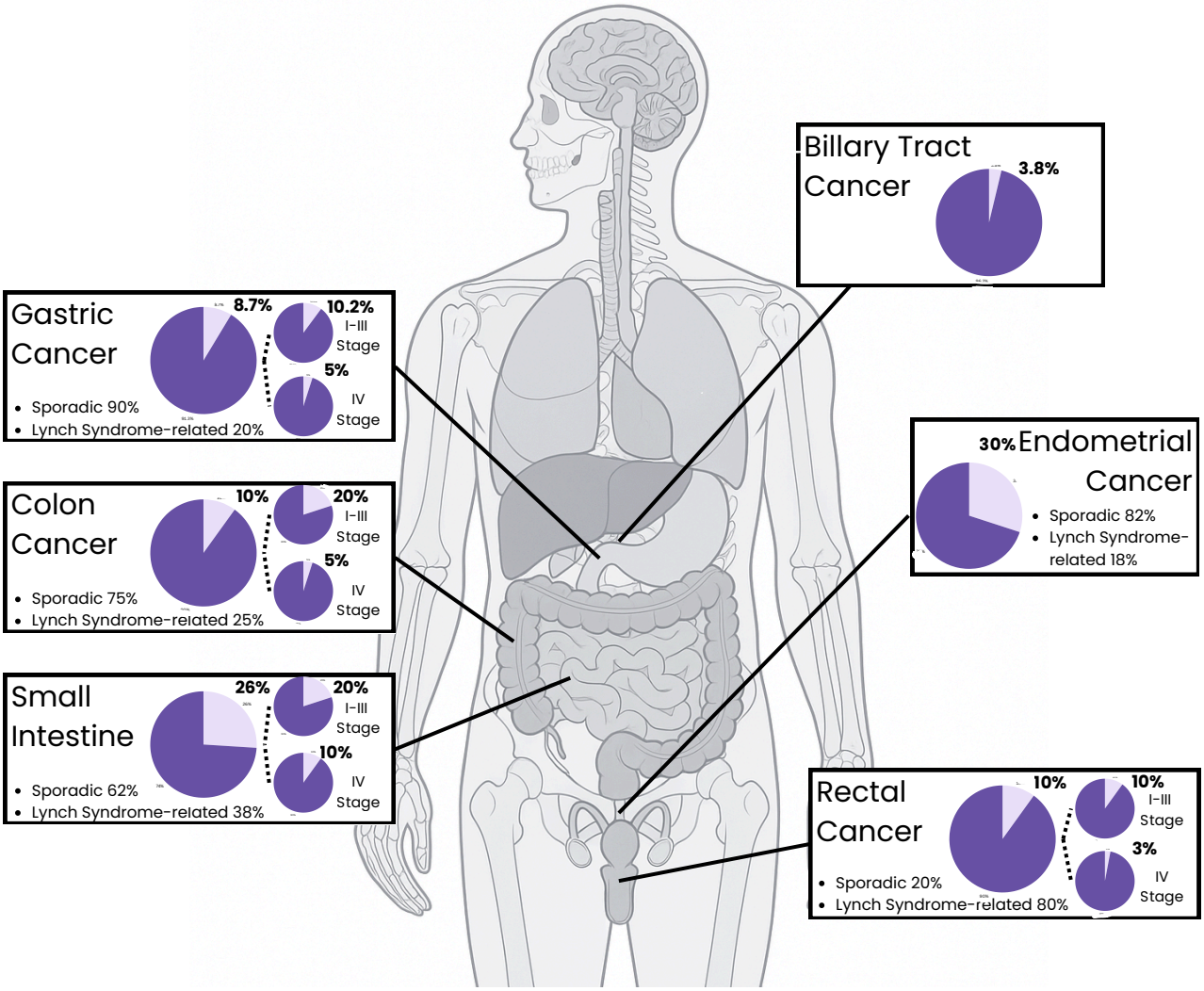


Illustration adapted from Ambrosini et al. Nature Reviews Clinical Oncology 2025

Because the benefits of immunotherapy are so significant, identifying patients with MSI-high tumors — even in these less common cancer types — can dramatically impact treatment outcomes. MSI-high status predicts a better response to immune checkpoint inhibitors, offering these patients improved survival rates and quality of life compared to standard therapies. As immunotherapy continues to reshape the oncology landscape, comprehensive MSI testing ensures that no eligible patient is overlooked, regardless of how infrequently the biomarker appears in a given tumor type.

1. Biological Mechanism Behind MSI

1a. Mismatch Repair (MMR) System Dysfunction

The MMR system is responsible for maintaining genomic integrity by correcting replication errors, such as base-base mismatches and insertion-deletion loops (indels). The system primarily relies on two protein complexes: MutSα (MSH2/MSH6), which detects mismatches, and MutLα (MLH1/PMS2), which facilitates excision and repair. MMR deficiency typically arises from two classical mechanisms:

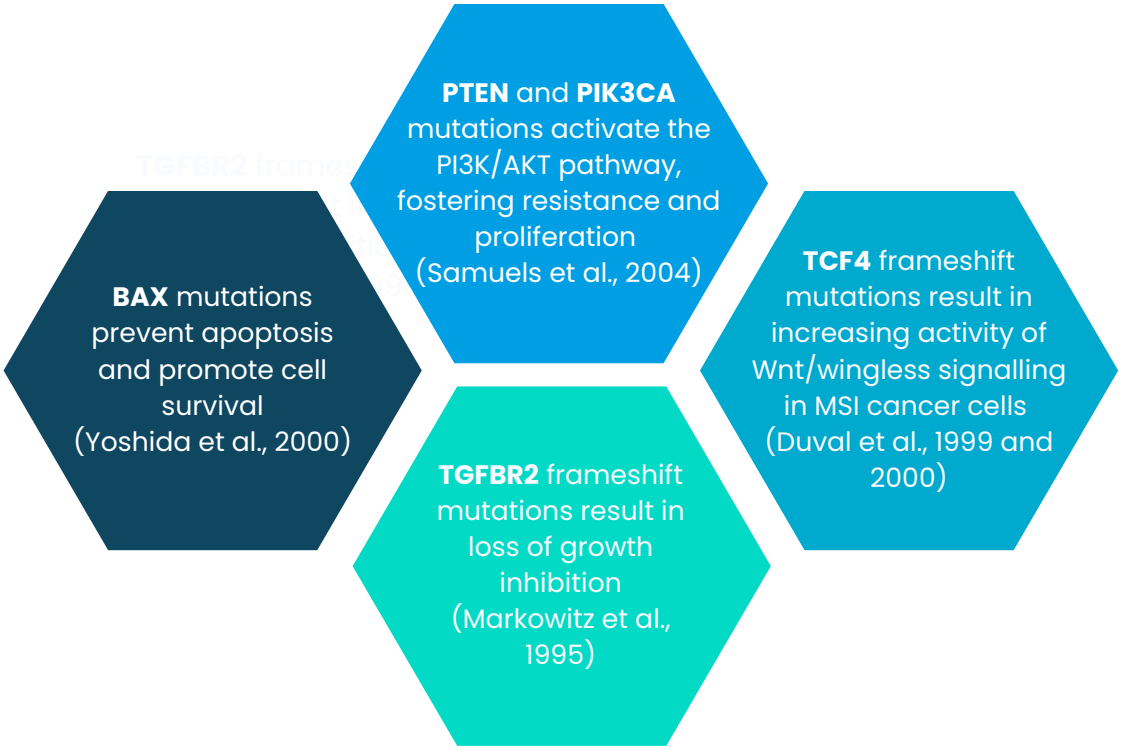
- **Germline mutations** in MMR genes (as seen in Lynch syndrome), or
- **Somatic inactivation** via mutations or epigenetic silencing, particularly promoter hypermethylation of *MLH1* (Boland & Goel, 2010).

When these proteins are inactivated, the DNA repair function is lost, allowing replication errors to accumulate unchecked. Importantly, studies have suggested that tumors with loss of MSH2 or MSH6 may exhibit a higher tumor mutational burden (TMB) compared to those with MLH1 or PMS2 loss, due to the upstream, primary role of the MutSα complex in mismatch detection and repair initiation (Goodman et al., 2017; Hause et al., 2016). However, this association remains complex and may vary depending on tumor type and specific mutation context.

1b. Key Molecular Pathways Affected by MSI

MSI results from MMR deficiency and leads to widespread accumulation of somatic mutations, particularly frameshift mutations in microsatellite regions. These mutations affect numerous pathways simultaneously, contributing to oncogenesis and influencing tumor behavior. Rather than being confined to a few genes, MSI impacts hundreds of coding regions, leading to a highly heterogeneous mutational landscape (Jonchère et al., 2018).

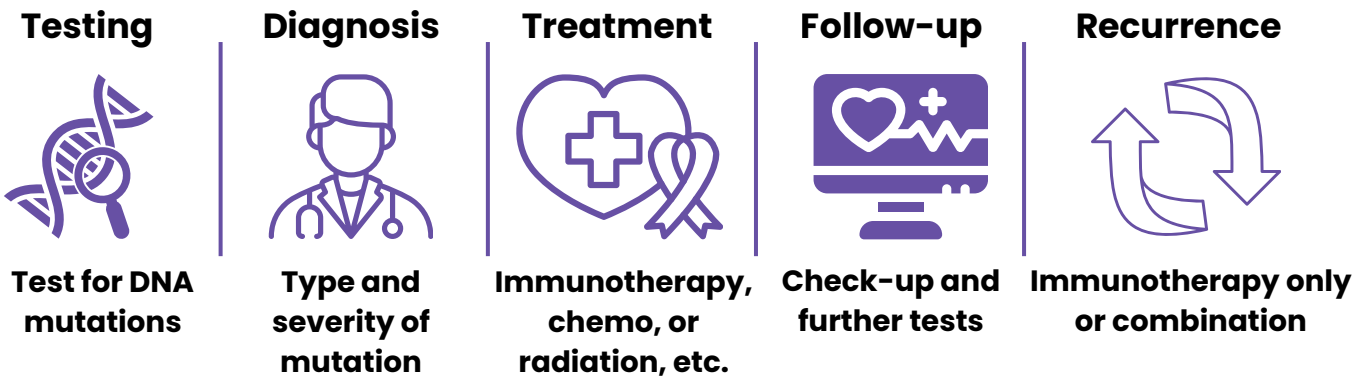
Meta-analyses of exome sequencing data have revealed that MSI-induced mutations often converge on crucial oncogenic pathways. These include:



However, these are examples within a broader and highly variable context, as MSI induces a high load of passenger and driver mutations across multiple oncogenic processes. Furthermore, MSI-related frameshift mutations generate abundant novel neoantigens, enhancing tumor immunogenicity and partly explaining the favorable prognosis observed in MSI-high tumors (Boland & Goel, 2010; Bonneville et al., 2017). Beyond immunogenicity, MSI-induced toxic mutations — leading to loss-of-function in essential genes — have also been proposed to contribute to the good prognosis of these tumors, independent of immune responses (Dorard et al., 2011; Collura et al., 2014).

2. Prognostic and Therapeutic Implications of MSI

MSI Status Provides Critical Insights Throughout the Entire Patient Journey



MSI status has clear prognostic value, especially in early-stage colorectal and endometrial cancers. A meta-analysis by Vilar & Gruber (2010) showed that MSI-H stage II CRC patients had significantly lower recurrence rates and better overall survival than their MSS counterparts. However, they also derive limited benefit from 5-FU-based chemotherapy, likely due to reduced recognition of drug-induced DNA damage.

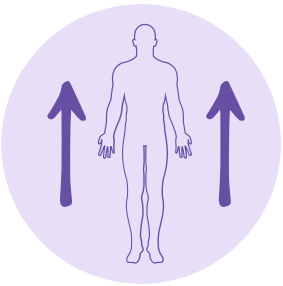
In metastatic colorectal cancer (mCRC), the landscape shifted dramatically following pivotal trials. The KEYNOTE-177 study (André et al., 2020) found that pembrolizumab doubled progression-free survival versus chemotherapy as a first-line treatment in MSI-H mCRC patients, with fewer adverse events and higher quality-of-life scores. Similarly, the CheckMate-8HW trial (Andre et al., 2024) demonstrated superior PFS for nivolumab plus ipilimumab versus chemotherapy (HR: 0.32) in the same population.

2a. Prognostic Significance of MSI

MSI status plays a crucial role in predicting patient outcomes across various cancer types.

Improved Prognosis in MSI-High Cancers

MSI-high colorectal and endometrial cancers generally have a more favorable prognosis than microsatellite stable (MSS) tumors. The increased presence of tumor-infiltrating lymphocytes (TILs) enhances anti-tumor immunity, contributing to longer overall survival (Vilar & Gruber, 2010). Moreover, MSI leads to frameshift mutations that can generate abnormal splicing events, including the production of non-functional isoforms such as HSP110ΔE9, which further sensitize tumors to immune surveillance (Dorard et al., 2011; Collura et al., 2014).



Variable Prognosis in MSI-High Gastric Cancers

Unlike colorectal cancer, the prognostic impact of MSI-high status in gastric cancer is more nuanced. Early-stage MSI-high tumors generally show better survival rates, particularly in the absence of adjuvant chemotherapy. However, in advanced stages, the benefit diminishes, and MSI-high tumors may not respond well to conventional chemotherapy regimens, sometimes exhibiting more aggressive behavior (Kim et al., 2018).

2b. Therapeutic Implications of MSI

Chemotherapy Resistance

MSI-high colorectal cancers often demonstrate primary resistance to 5-fluorouracil (5-FU)-based chemotherapy. This has led to a shift in treatment paradigms, favoring immune-based therapies over traditional chemotherapy for MSI-high patients (Ribic et al., 2003).

Immunotherapy Response

MSI-high tumors exhibit high tumor mutational burden (TMB), leading to enhanced sensitivity to immune checkpoint inhibitors such as pembrolizumab and nivolumab. These drugs target the PD-1/PD-L1 axis, reactivating the immune system to recognize and attack cancer cells (Le et al., 2015).

Targeted Therapy Limitations and Opportunities

MSI status can influence the effectiveness of certain targeted therapies. MSI-high tumors often exhibit distinct molecular features—such as BRAF or KRAS mutations—that may predict limited response to EGFR-targeted agents like cetuximab or panitumumab in colorectal cancer (De Roock et al., 2010). However, ongoing research suggests MSI may also create new therapeutic opportunities, including combination strategies that pair targeted agents with immunotherapy to overcome resistance mechanisms.

Immunotheray Treatments Approval Associated with MSI/dMMR Status

Drug	Indications	Tumor Types	Testing Requirement	Approval
Pembrolizumab	MSI-H/dMMR mCRC (first-line), Endometrial carcinoma, Solid tumors (accelerated approval)	Colorectal, Endometrial, Other solid tumors	MSI-H or dMMR confirmation	FDA, EMA, PMDA
Nivolumab	MSI-H/dMMR metastatic CRC post-chemotherapy	Colorectal	MSI-H or dMMR confirmation	FDA
Nivolumab + Ipilimumab	1L metastatic CRC MSI-H/dMMR, or after chemo	Colorectal	MSI-H or dMMR confirmation	FDA, EMA, PMDA
Dostarlimab	Recurrent/advanced dMMR/MSI-H Endometrial carcinoma post-platinum therapy	Endometrial	MSI-H or dMMR confirmation	FDA, EMA
Durvalumab ± Chemo or Olaparib	Endometrial: dMMR (durva+chemo → durva); pMMR/MSS (durva+chemo → durva+olaparib)	Endometrial (advanced/ recurrent)	dMMR and pMMR	FDA, EMA

Based on FDA and EMA drug registration as of October 2025.

3. Conclusion

Microsatellite instability represents a powerful indicator of tumor behavior, prognosis, and therapeutic response. Understanding the biological origins and clinical implications of MSI is essential for advancing precision cancer care, ensuring appropriate treatment selection, and improving patient outcomes.

This first paper has outlined the scientific basis and clinical significance of MSI. The next installment in this series will focus on **MSI diagnostics** — including immunohistochemistry, molecular assays, next-generation sequencing, and key considerations for analytical accuracy and clinical implementation.

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About MSInsight

MSInsight is a French precision oncology company focused on the detection of MSI. Its software platform, MSIcare, uses next-generation sequencing (NGS) and bioinformatics to deliver accurate, standardized MSI results for solid tumors. Designed for clinical laboratories and backed by 20+ years of experience, MSIcare supports the integration of genomic biomarkers into routine diagnostics to improve treatment selection and patient outcomes.

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