

Hereditary nonpolyposis colorectal cancer

Lynch syndrome

Inherited DNA mismatch-repair deficiency and colorectal carcinogenesis

Genetics → Molecular pathology → Diagnosis → Clinical implications

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Learning objectives

- Define Lynch syndrome and distinguish it from a generic MSI-high tumor.
- Explain inherited susceptibility, the somatic second hit, and DNA mismatch-repair failure.
- Relate microsatellite instability to tumor development and morphology.
- Interpret MMR immunostaining patterns and appropriate follow-up testing.
- Connect molecular findings with hereditary-risk assessment and surveillance.

A hereditary colorectal cancer predisposition

- Lynch syndrome arises from an inherited pathogenic defect of DNA mismatch repair.
- Autosomal dominant transmission describes susceptibility in families.
- Cancer develops after additional somatic events disable effective mismatch repair.
- Unlike classic FAP, massive colorectal polyposis is not the defining phenotype.

Historical terminology: HNPCC and Lynch syndrome

- HNPCC is the historical descriptive term for familial colorectal cancer without florid polyposis.
- Lynch syndrome specifies the inherited mismatch-repair predisposition.
- The clinically important distinction is hereditary predisposition versus somatic MSI alone.

Frequency and teaching significance

- Lynch syndrome accounts for about 2%–4% of colorectal cancers.
- It is presented as the most common syndromic form of colon cancer.
- The syndrome illustrates how defective genome maintenance can drive epithelial neoplasia.

The colorectal distribution is often proximal

Typical pattern, not an anatomic diagnostic criterion

Right colon

Lynch-associated CRC: Often proximal;
May present at a younger age

Left colon

Sporadic CRC: Heterogeneous;
Not restricted to a single side

Anatomic distribution is a clue—not a standalone diagnostic criterion.

Age of presentation: Relative rather than absolute

- Lynch-associated colorectal cancer often occurs younger than typical sporadic cancer.
- A young patient with colorectal cancer should prompt attention to family history.
- Older age does not, by itself, exclude a hereditary predisposition.

Associated cancers extend beyond the colon

Sites described in the Robbins Lynch syndrome section

Colorectum

Endometrium

Stomach

Ovary

Ureter / urinary tract

Small bowel

Brain

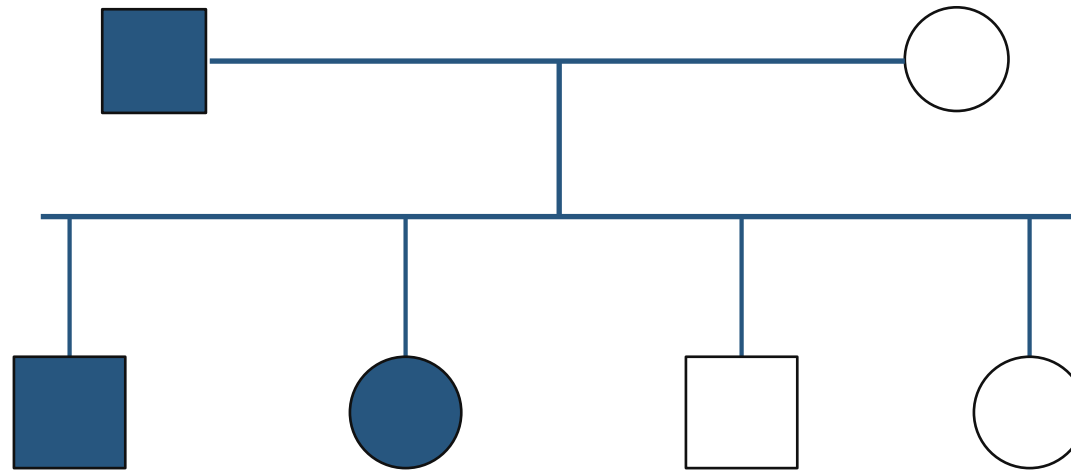
Hepatobiliary / pancreas / skin

Endometrial carcinoma is central to the syndrome

- A family may exhibit colorectal and endometrial cancers across generations.
- The pattern reflects a shared inherited DNA-repair susceptibility.
- A gastrointestinal-only pedigree can miss an important hereditary clue.

Autosomal dominant susceptibility

Pedigree illustration; Not a simulated epidemiologic cohort

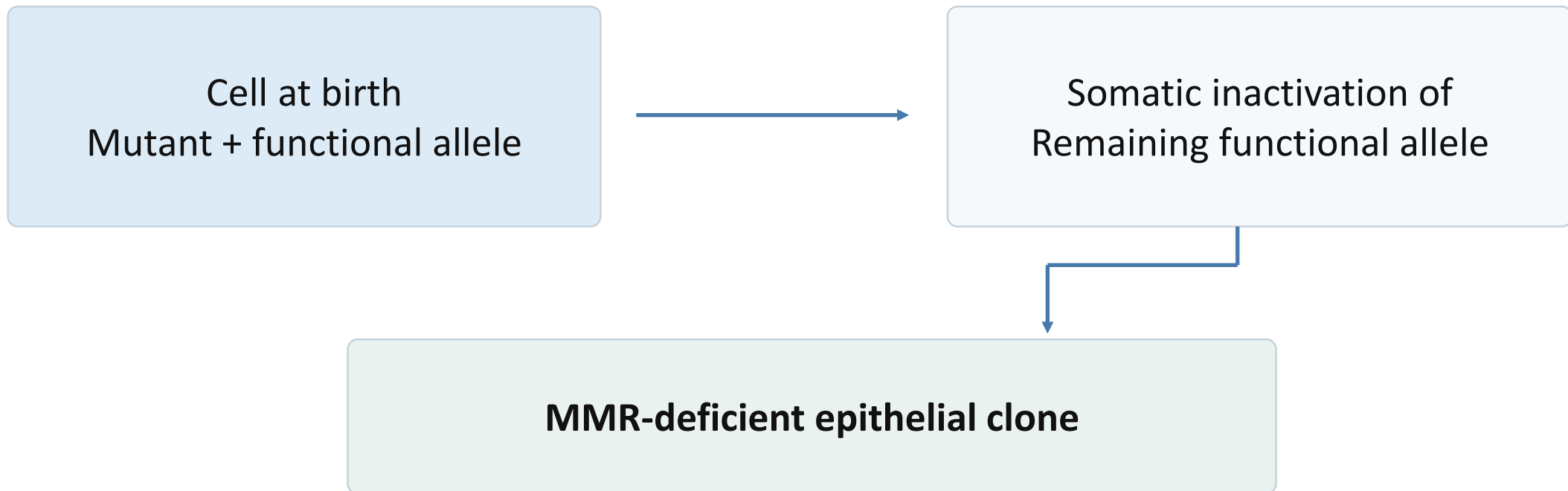


Illustrative inheritance: Carrier offspring shown in blue; Not a penetrance prediction.

Each child of a heterozygous carrier has a 50% inheritance probability.

The inherited allele is the first hit

Tumor development requires loss of the remaining functional repair capacity

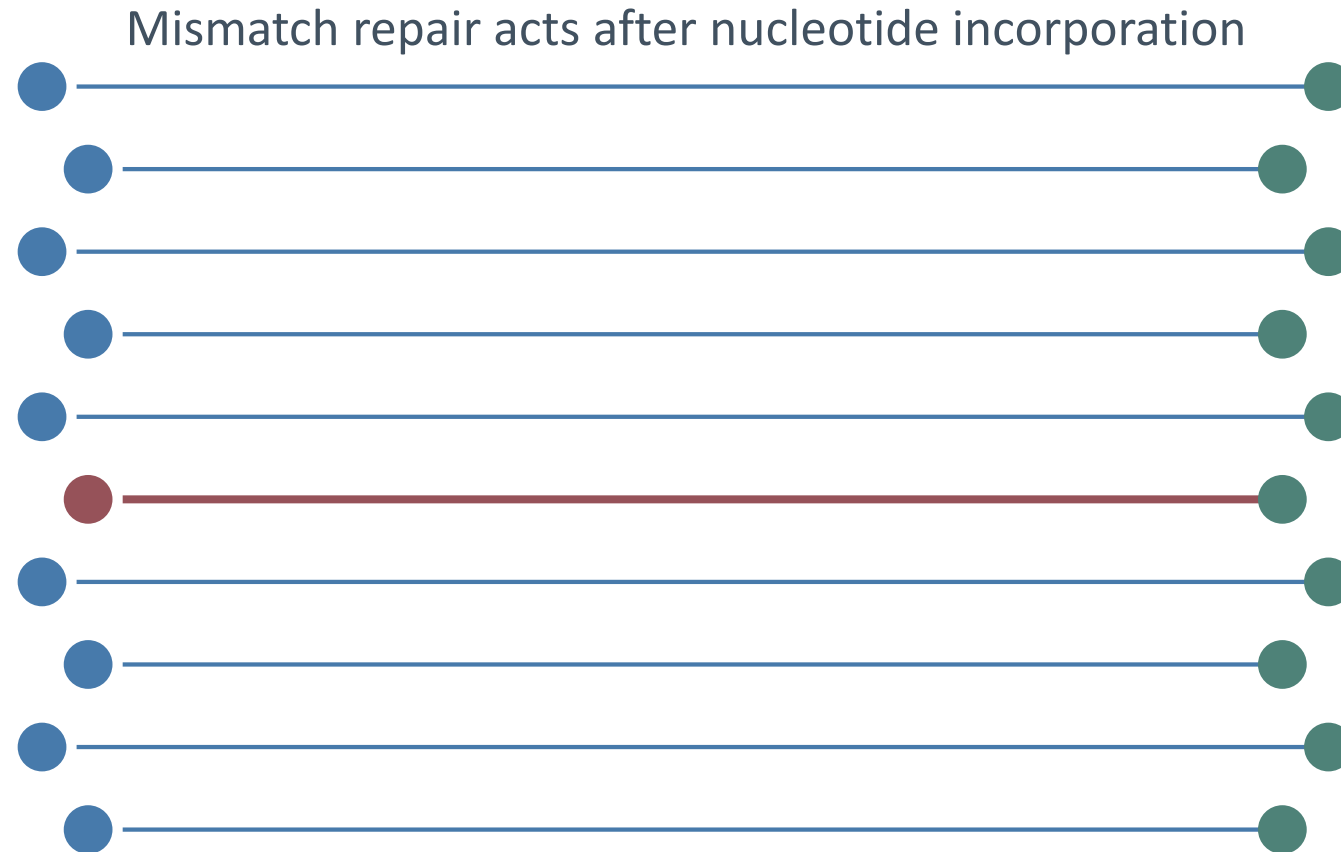


Autosomal dominant inheritance of susceptibility; Tumor initiation involves biallelic loss.

Why “nonpolyposis” matters

- A patient can develop colorectal carcinoma without the profuse adenomas typical of classic FAP.
- Absence of hundreds of polyps does not imply absence of inherited risk.
- Clinical suspicion must incorporate the cancer pattern and tumor molecular findings.

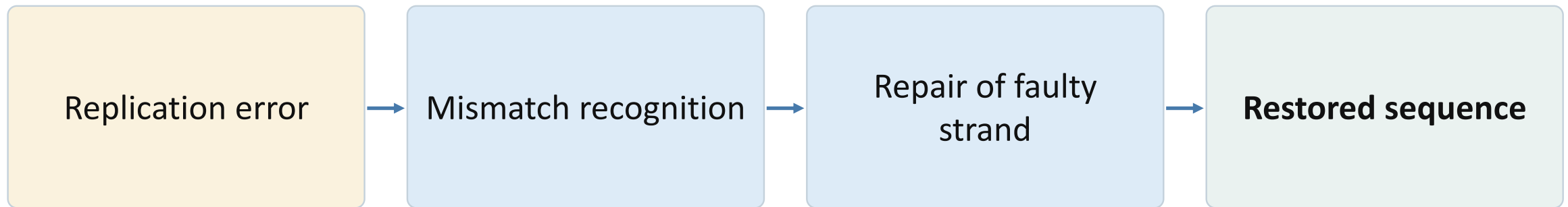
Normal DNA replication creates repairable errors



DNA polymerase occasionally mispairs or slips

A functional repair system corrects mismatches

Simplified repair sequence, not a complete protein-interaction pathway



Deficient mismatch repair allows sequence errors to persist and accumulate.

Microsatellites: Short repeated sequences

- Microsatellites contain short, tandemly repeated DNA motifs.
- Repeat regions are particularly susceptible to replication slippage.
- Functional mismatch repair normally prevents persistent insertion/deletion errors.

Microsatellite instability is a length change

Schematic repeats; Not patient-derived electropherograms or sequencing data

Normal DNA replication

A C A C A C A C

A C A C A C A C

A C A C A C A C

Stable repeat length

Unrepaired replication slippage

A C A C A C A C

A C A C A C A C A C

A C A C A C

Different repeat lengths across clones

Loss of repair function destabilizes the genome

- Following biallelic inactivation of an MMR gene, replication errors persist.
- Repetitive DNA sequences accumulate insertion/deletion changes.
- A greatly increased mutation rate following repair loss.

Two major mismatch-repair protein partnerships

Contemporary molecular diagnostic framework

MSH2–MSH6 complex
Mismatch recognition



MLH1–PMS2 complex
Downstream repair coordination

Core screening panel: MLH1 • PMS2 • MSH2 • MSH6

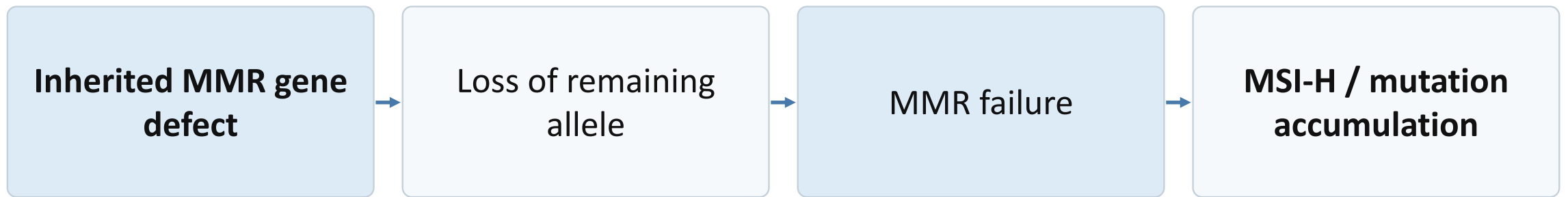
Protein partnerships help interpret paired loss on immunohistochemistry.

Core hereditary genes

- MLH1 and MSH2 in its introductory section.
- Contemporary Lynch genetic panels also include MSH6 and PMS2.
- Germline EPCAM deletions can cause functional MSH2 inactivation.

From germline predisposition to MSI

A pathway model of Lynch-associated carcinogenesis



Not all repetitive sequences are coding

- Many microsatellites lie outside protein-coding DNA.
- Some repeats occur within genes affecting growth regulation or cell survival.
- Thus MSI is both a measurable genomic phenotype and a potential route to driver mutations.

Examples of downstream driver targets

Frameshift mechanisms emphasized colorectal carcinogenesis

TGFBR2 frameshift



Reduced growth inhibition

BAX frameshift



Reduced apoptosis

Illustrative targets; Mutations accumulate across multiple genes.

TGFB2: Loss of a growth-inhibitory signal

- TGFB2 encodes the type II receptor for transforming growth factor- β .
- In normal colonic epithelium, TGF- β signaling restrains proliferation.
- Mutation may weaken this brake and favor expansion of abnormal epithelial clones.

BAX: Impairment of apoptosis

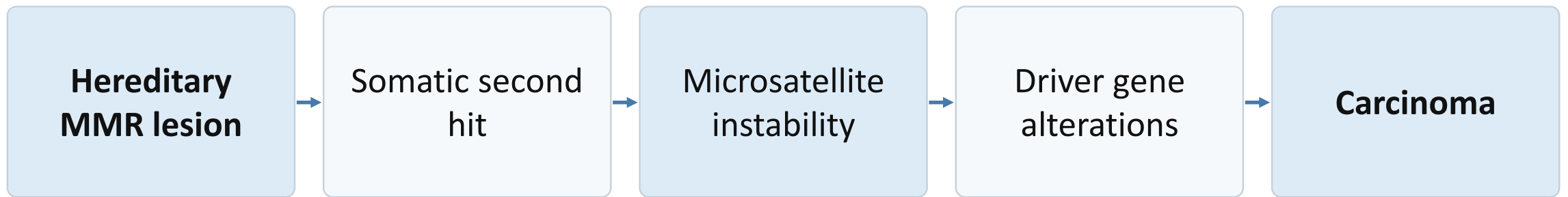
- BAX encodes a pro-apoptotic protein.
- Loss-of-function mutations may allow damaged cells to survive.
- Cancer evolution can therefore couple increased proliferation with diminished cell death.

Mutational burden is not the whole mechanism

- Genomic instability creates diversity; Selection favors particular cellular traits.
- Not every microsatellite mutation is a driver of neoplasia.
- Progression requires advantageous alterations in growth and survival pathways.

Lynch-associated colorectal carcinogenesis

Causal summary of the core molecular pathway



Three pathways dominate colorectal carcinogenesis

Mechanistic classification in the adjacent Robbins adenocarcinoma section

APC / β -catenin pathway

MMR deficiency → MSI-H

CIMP / MLH1 silencing

These are mechanistic categories; Their molecular and epigenetic features can overlap.

The conventional APC/Wnt pathway differs

- Early APC loss activates β -catenin–dependent proliferation.
- Additional changes, including KRAS and TP53 abnormalities, accumulate during progression.
- MMR deficiency and MSI define a different principal mechanistic route.

The CpG island methylator phenotype

- CIMP is associated with methylation-mediated gene silencing.
- Somatic MLH1 promoter hypermethylation can disable mismatch repair.
- The resulting tumor can be MSI-high without an inherited pathogenic MMR variant.

Hereditary and sporadic tumors can both be MSI-high

Shared phenotype; Different underlying etiologies

Inherited pathogenic MMR variant

Somatic MLH1 promoter methylation

DMMR / MSI-H tumor

An MSI-high phenotype is not equivalent to a Lynch syndrome diagnosis.

BRAF and MLH1 methylation help with triage

- In colorectal cancer, BRAF alteration and MLH1 promoter methylation favor a sporadic MLH1-silenced pathway.
- These findings help interpret loss of MLH1/PMS2 staining.
- They do not replace integrated assessment of family history and germline testing.

Reflex testing after MLH1/PMS2 loss

Contemporary colorectal-tumor interpretation

Tumor: MLH1 / PMS2 loss



Reflex MLH1 promoter methylation
And/or BRAF analysis (CRC)

Methylation / BRAF variant supports a sporadic mechanism; Consider pedigree and full context.

BRAF reflex testing is for colorectal cancers, not an all-organ rule.

Why MSI does not equal Lynch syndrome

- Lynch syndrome is a germline predisposition diagnosis.
- MSI-high is a tumor molecular phenotype that has more than one possible cause.
- Tumor testing identifies candidates for inherited-risk evaluation; It is not itself a germline result.

Morphologic correlations with MSI-high CRC

- MSI-associated colorectal cancers are frequently right-sided.
- Mucinous differentiation is relatively frequent.
- A conspicuous lymphocytic reaction may occur within or around the tumor.

Mucinous morphology: How to interpret it

- Extracellular mucin and floating malignant cells may characterize a mucinous carcinoma.
- Mucinous differentiation is a morphologic clue, not proof of Lynch syndrome.
- Direct histologic assessment remains necessary; A schematic cannot substitute for H&E.

Tumor-infiltrating lymphocytes: Interpretation

- Prominent intratumoral or peritumoral lymphocytes may accompany MSI-high CRC.
- A lymphocyte-rich tumor can suggest the need to review tumor MMR/MSI status.
- Inflammation is nonspecific and cannot assign hereditary versus sporadic origin.

Serrated lesions and molecular heterogeneity

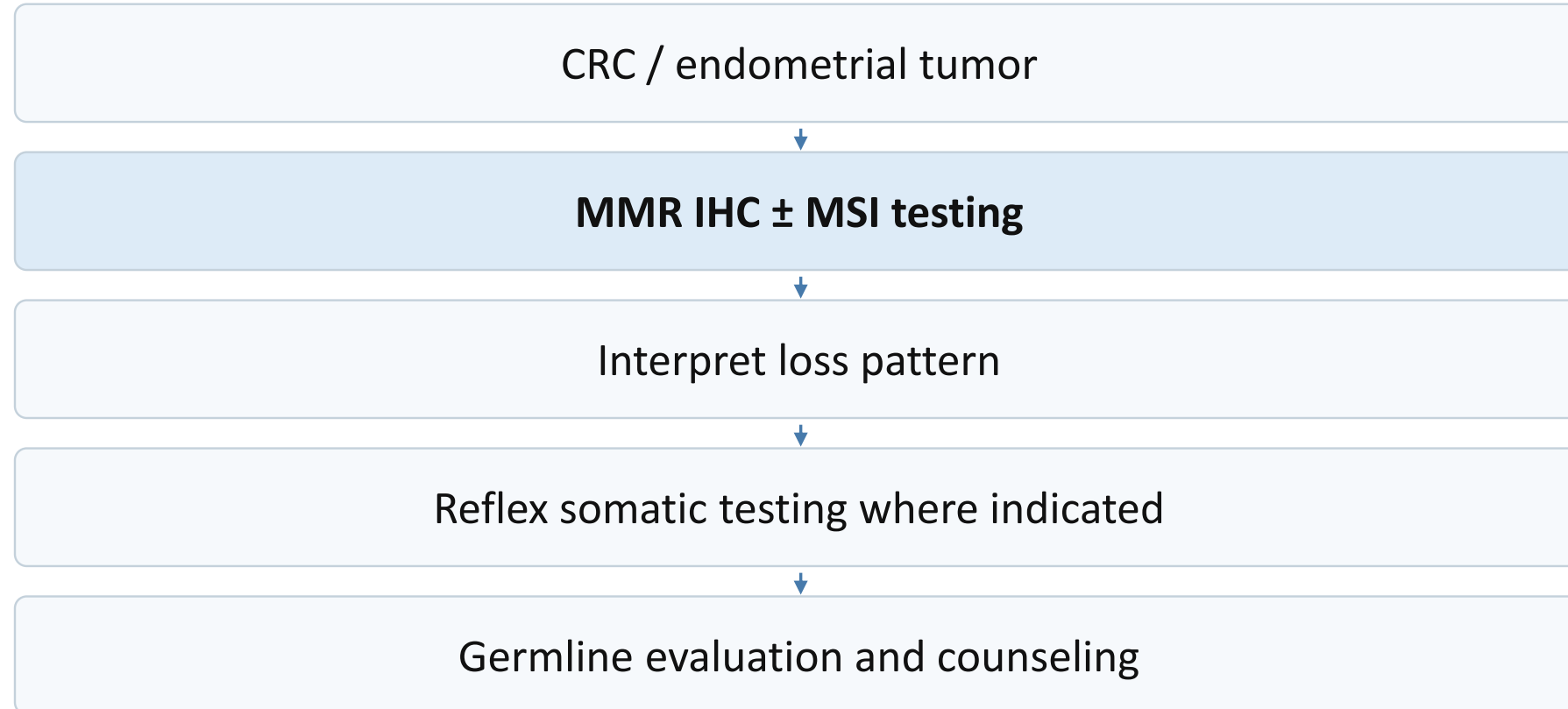
- MSI in association with sessile serrated lesions and cancers arising from them.
- This association is not a pathognomonic precursor pattern for Lynch syndrome.
- A serrated lesion by itself does not establish inherited mismatch-repair deficiency.

Morphology cannot specify the germline cause

- MSI-associated histology suggests a biological phenotype.
- Mucin, lymphocytes, right-sided location, and poor differentiation are individually nonspecific.
- IHC/MSI and genetic investigations are required for etiologic clarification.

A structured tumor-to-germline evaluation

Typical clinical pathology pathway, simplified; Test selection is context-dependent



MMR immunohistochemistry: The four proteins

- Tumor tissue is assessed for nuclear MLH1, PMS2, MSH2, and MSH6.
- Loss of tumor nuclear staining with retained internal controls indicates abnormal protein expression.
- An interpretable IHC pattern directs the next diagnostic step.

Paired loss of MLH1 and PMS2

Commonly prompts somatic MLH1-silencing workup in colorectal cancer

MLH1

PMS2

MSH2

MSH6

Lost

Lost

Retained

Retained

Consider MLH1 methylation and/or BRAF testing before hereditary attribution.

Evaluate tumor-cell nuclei with intact nuclear staining in internal controls.

Paired loss of MSH2 and MSH6

Suggests assessment of MSH2 and EPCAM-associated mechanisms

MLH1	PMS2	MSH2	MSH6
Retained	Retained	Lost	Lost

Hereditary MSH2 or EPCAM alteration is one possibility; Confirm with genetic evaluation.

Evaluate tumor-cell nuclei with intact nuclear staining in internal controls.

Isolated MSH6 loss

Assess whether tumor treatment or technical factors could affect interpretation

MLH1

PMS2

MSH2

MSH6

Retained

Retained

Retained

Lost

An isolated pattern can direct germline assessment of MSH6.

Evaluate tumor-cell nuclei with intact nuclear staining in internal controls.

Isolated PMS2 loss

Reconsider pattern, controls, and the appropriate genetics pathway

MLH1

PMS2

MSH2

MSH6

Retained

Lost

Retained

Retained

PMS2-associated Lynch syndrome is a possibility, not a diagnosis from IHC alone.

Evaluate tumor-cell nuclei with intact nuclear staining in internal controls.

Internal controls determine IHC validity

- Non-neoplastic epithelium, lymphocytes, or stromal cells should retain expected nuclear expression.
- A globally unstained section is technically uninterpretable.
- Focal, heterogeneous, or treatment-related patterns may require review and additional testing.

Molecular microsatellite-instability testing

- Tumor microsatellite lengths are evaluated with a validated molecular assay.
- Instability at multiple informative markers supports the MSI-high phenotype.
- Assay methodology and interpretation thresholds depend on the validated laboratory platform.

IHC and MSI answer related, different questions

MMR protein IHC

- Shows loss or retention of protein expression
- Provides a pattern suggesting specific genes

MSI molecular testing

- Demonstrates repeat-length instability
- Does not directly identify an inherited allele

Discordant or uninterpretable results warrant integrated molecular-pathology review.

Somatic and germline testing must be distinguished

- Tumor-only sequencing can reveal acquired alterations.
- Germline testing evaluates constitutional pathogenic variants.
- Double-somatic MMR inactivation can explain some Lynch-like tumors with negative germline testing.

A negative hereditary test may not close the case

- Interpret results in relation to tumor phenotype and family history.
- Variant interpretation and detection limits can complicate risk classification.
- Hereditary-risk assessment may be indicated despite inconclusive tumor testing.

Lynch syndrome versus classic FAP

Feature	Lynch syndrome	Classic FAP
Central mechanism	Mismatch repair → MSI	APC/Wnt dysregulation
Typical adenoma burden	Not massive polyposis	Numerous adenomas
Key inherited genes	MLH1, MSH2, etc.	APC
Transmission	Autosomal dominant	Autosomal dominant

Both predispose to colorectal cancer but through different molecular mechanisms.

Lynch syndrome versus MUTYH polyposis

Feature	Lynch syndrome	MUTYH polyposis
DNA repair	Mismatch repair	Base-excision repair
Inheritance	Autosomal dominant	Autosomal recessive
Polyp burden	Not classic polyposis	Often fewer than classic FAP
Genetic hallmark	MMR gene alteration	Biallelic MUTYH

Diagnostic clues are not definitive tests

Finding	Supports LS evaluation	Not sufficient alone
Early CRC	Yes	Age does not confirm germline cause
Right-sided CRC	Suggestive	Common in sporadic MSI too
MSI-high tumor	Requires etiologic workup	Can be caused by MLH1 methylation
MMR protein loss	Directs investigation	May be double somatic

Use phenotype + tumor molecular data + family history + appropriate germline testing.

Family history changes the next step

- Record colorectal and extracolonic cancers across maternal and paternal lineages.
- Age at diagnosis and multiple primaries sharpen suspicion.
- A small or incompletely known pedigree cannot reliably exclude Lynch syndrome.

Genetic counseling and cascade testing

- A confirmed pathogenic germline variant can guide targeted testing of relatives.
- First-degree relatives can be offered counseling and familial-variant testing.
- Disease penetrance varies: Absence of cancer does not mean an at-risk relative is not a carrier.

Clinical risk: More than an index tumor

- Individuals with Lynch syndrome remain at risk for additional colorectal and extracolonic primaries.
- These risks make identification of a germline variant clinically actionable.
- Surveillance planning should consider the gene, individual history, and family context.

Surveillance is gene- and history-dependent

- GeneReviews describes intensive colonoscopic surveillance with removal of premalignant polyps.
- Recommended starting age and interval vary by the implicated MMR gene.
- Clinical schedules require current guideline review and specialist individualization.

Gynecologic risk management

- Teach patients about abnormal uterine bleeding and other concerning symptoms.
- Discuss risk-reducing gynecologic options with appropriate specialists after childbearing.
- Evidence for some gynecologic screening strategies is limited; Avoid equating screening with prevention.

Other organ systems require selective assessment

- Consider gastrointestinal, urinary tract, pancreatic and other syndrome-related risks.
- Additional surveillance is not identical for every carrier.
- Individual gene, ancestry, family history, and guideline evidence affect decisions.

Checkpoint blockade and the MSI phenotype

- MSI-high colorectal cancers as more responsive to checkpoint inhibitors.
- The predictive biomarker pertains to tumor dMMR/MSI status, not simply to the family history.
- Treatment choices also depend on tumor setting and contemporary oncology standards.

Do not confuse hereditary risk and tumor stage

- Lynch syndrome identifies an inherited susceptibility pathway.
- TNM stage describes local invasion, regional nodes, and distant disease.
- Therapy requires both tumor staging and molecular assessment where indicated.

Case 1: Young patient with right-sided carcinoma

HYPOTHETICAL TEACHING CASE

A young adult undergoes resection of a right-sided colorectal adenocarcinoma. MMR IHC shows tumor-cell loss of MSH2 and MSH6, with retained expression in internal controls.

Which hereditary genes or mechanisms merit evaluation?

Case 1: Interpretation

- Paired MSH2/MSH6 loss suggests an MSH2–EPCAM-related defect, among other possibilities.
- Refer for genetic counseling and appropriate germline testing.
- This IHC finding is a screening clue, not proof of a germline pathogenic variant.

Case 2: A sporadic mimic

HYPOTHETICAL TEACHING CASE

An older patient has a proximal MSI-high colorectal carcinoma. IHC shows loss of MLH1 and PMS2. Additional tumor studies identify MLH1 promoter hypermethylation.

Does MSI-high status establish Lynch syndrome?

Case 2: Interpretation

- Somatic MLH1 promoter methylation supports a sporadic dMMR pathway.
- Germline attribution requires the full clinical and molecular context.
- MSI and MMR protein loss describe tumor biology, not inheritance by themselves.

Case 3: The family-history clue

HYPOTHETICAL TEACHING CASE

An individual reports colorectal carcinoma in a parent and endometrial carcinoma in another close relative. Their own colorectal tumor has not been characterized.

What information and tests should be prioritized?

Case 3: Integrated approach

- Construct a cancer pedigree including age at diagnosis and affected tissue.
- Obtain tumor MMR/MSI testing when appropriate and available.
- Use genetic counseling to determine an informative germline testing strategy.

Five diagnostic principles to retain

- Lynch syndrome is an inherited mismatch-repair predisposition.
- The second hit creates a repair-deficient clone.
- MSI-high tumors can arise by inherited or sporadic mechanisms.
- IHC/MSI testing identifies a phenotype and directs further investigations.
- Germline confirmation has consequences for surveillance and relatives.

Primary and supplementary references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 17, pp. 739–743.
- GeneReviews: Lynch Syndrome (NCBI Bookshelf NBK1211), contemporary genetic testing and surveillance.
- NCI PDQ: Genetics of Colorectal Cancer, molecular diagnostic differentiation.
- Clinical vignettes are hypothetical; no synthetic histology is shown.