PIPADOR REVISION

MRCOG Part 1 Revision Notes

Lynch Syndrome

CELL BIOLOGY • LECTURE 124

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 124: Lynch Syndrome

Cell biology • Visual revision edition — follows Lecture 123 (HBOC)

COLOUR CODE USED THROUGHOUT THESE NOTES

MLH1 / ENDOMETRIAL	MSH2 / BOWEL	MSH6 / OVARIAN	PMS2	SPORADIC / TREATMENT

LEARNING OBJECTIVES — tick off as you go

- ☐ Explain mismatch repair, MSI and how IHC pairs guide testing.
- ☐ Quote gene-specific cancer risks, especially endometrial.
- ☐ Apply the universal endometrial tumour-testing algorithm.
- ☐ Plan surveillance, risk-reducing surgery and aspirin by gene.
- ☐ Know immunotherapy, variants (Muir–Torre, CMMRD) and reproductive issues.

1 Genetics

IN ONE LINE: *Germline loss of one mismatch-repair gene (MLH1, MSH2, MSH6, PMS2 or EPCAM) — AD, ~1 in 300. Tumours lose the second copy → microsatellite instability. The commonest inherited cause of endometrial cancer.*

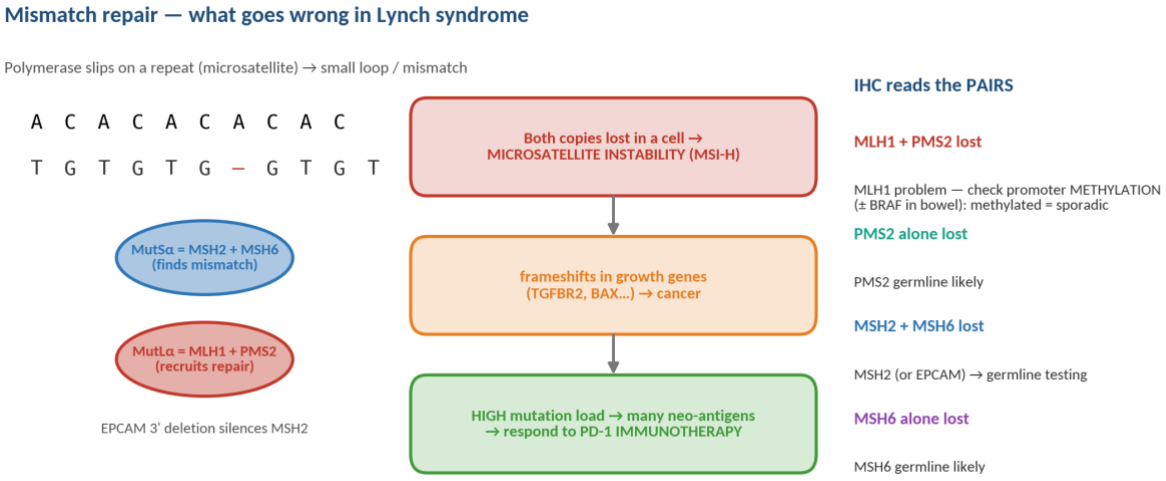
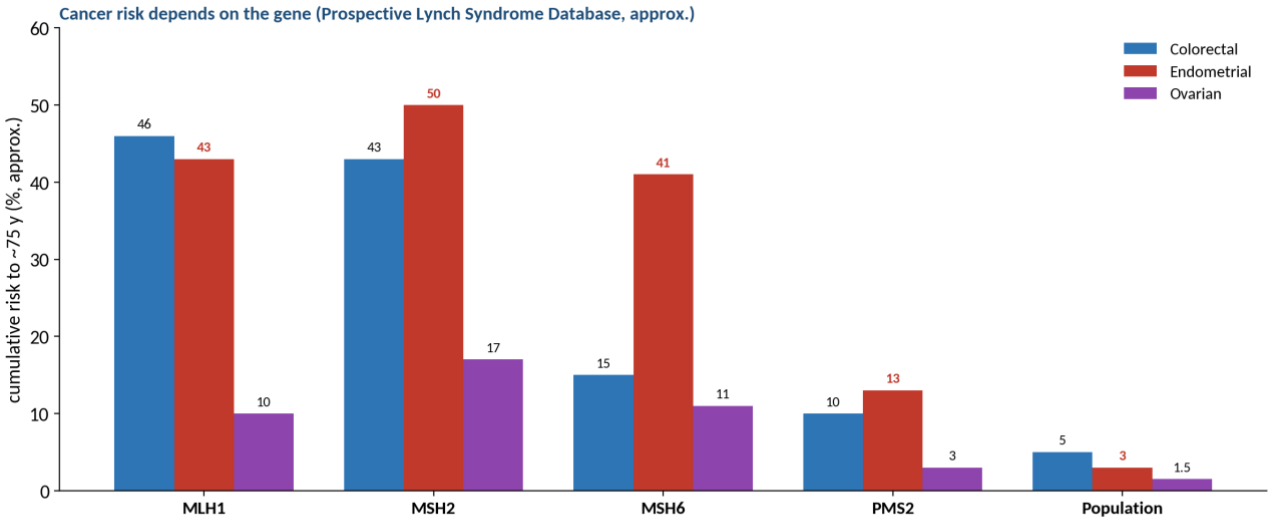


Figure 1. Mismatch repair, MSI and IHC pairs.

MNEMONIC / MEMORY HOOK

'Lynch genes: My Mum Makes Pies' — MLH1, MSH2, MSH6, PMS2 (+ EPCAM); partners pair up: MLH1–PMS2, MSH2–MSH6.

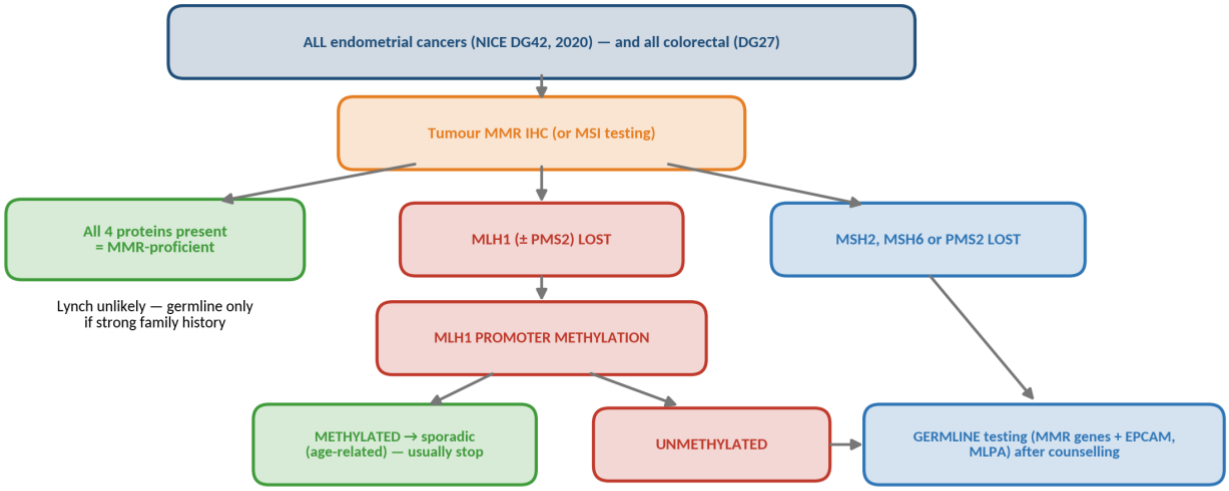
2 Cancer Risks



Women: ENDOMETRIAL cancer is as likely as bowel cancer and often the SENTINEL cancer (~50% present first with it, younger, endometrioid; lower uterine segment).
Ovarian: endometrioid/clear cell, often early stage. Others (MLH1/MSH2): gastric, small bowel, urothelial (MSH2), hepatobiliary, pancreas, brain, sebaceous.

Figure 2. Risk by gene.

3 Universal Tumour Testing



No germline variant but dMMR (unmethylated) → 'Lynch-like': test the TUMOUR for double somatic MMR hits; manage on family history.
Germline variant found → CASCADE testing of relatives; surveillance; risk-reducing surgery; immunotherapy eligibility if advanced.

Figure 3. Endometrial cancer MMR testing pathway.

- **Clinical criteria** (Amsterdam II, revised Bethesda) miss many carriers — now support suspicion only; universal tumour testing is standard.

4 Surveillance and Risk Reduction

Surveillance and risk reduction by gene (UK: BSG/ACPGBI 2020, Manchester consensus 2019)

	Colonoscopy (2-yearly)	Hysterectomy + BSO	Notes
MLH1	from 25	offer from ~35–40 (family complete)	highest bowel risk
MSH2 / EPCAM	from 25	offer from ~35–40	highest endometrial/ovarian; urinary tract
MSH6	from 35	offer from ~40	endometrial risk high; bowel lower
PMS2	from 35	hysterectomy optional (lower risk); ovarian risk low	lowest risks overall

- Routine gynae SCREENING (TVUS, pipelle, CA-125) is NOT recommended — no proven benefit; teach symptoms (abnormal/postmenopausal bleeding) → urgent assessment.
- After risk-reducing surgery: HRT (oestrogen-only after hysterectomy) until ~51. • Aspirin daily (NICE NG151): CAPP2 600 mg halved bowel cancer; optimal dose being studied (CaPP3) — discuss dose and bleeding risk. • H. pylori test and treat; upper GI endoscopy per gastro guidance. • Two-hit: CMMRD if both parents carriers.

Figure 4. Management by gene.

5 Treatment, Variants and Reproduction

Treatment, variants and reproduction

IMMUNOTHERAPY

- dMMR / MSI-H tumours → many neo-antigens → PD-1 blockade works
- endometrial: DOSTARLIMAB (+ chemo), pembrolizumab; colorectal: pembrolizumab (KEYNOTE-177); tissue-agnostic
- MMR status now part of endometrial molecular classification (POLE, dMMR, p53abn, NSMP)

VARIANTS + MIMICS

- MUIR–TORRE: sebaceous adenoma/ carcinoma, keratoacanthoma (often MSH2)
- CMMRD: BIALLELIC MMR (AR) → childhood brain, blood, bowel cancers + café-au-lait
- Familial CRC type X: Amsterdam + MMR-proficient; FAP / MUTYH polyposis; sporadic MLH1-methylated cancers

REPRODUCTION + PREGNANCY

- complete family before risk-reducing surgery; 50% transmission; PGT-M (HFEA-approved) or PND
- pregnancy: routine care; colonoscopy if needed (2nd trimester); LOW-dose aspirin acceptable — avoid high doses
- both partners carriers → 25% CMMRD → counsel

Figure 5. Immunotherapy, variants, reproduction.

★ PEARL

Every endometrial cancer gets MMR IHC (NICE DG42). MLH1 loss → methylation test; unmethylated or MSH2/MSH6/PMS2 loss → germline testing.

Endometrial cancer is often the sentinel cancer in women with Lynch. Gynae screening is not recommended — risk-reducing hysterectomy + BSO from ~35–40 (gene-dependent).

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

~1 in 300 Carrier frequency	**~40–50%** Endometrial (MLH1/MSH2/MSH6)	**~13%** Endometrial (PMS2)	**~17%** Ovarian (MSH2)

25 / 35 Colonoscopy start (MLH1/MSH2 vs MSH6/PMS2)	**2-yearly** Colonoscopy interval	**35–40** Hysterectomy + BSO	**~50%** CRC ↓ with aspirin (CAPP2)

HIGH-YIELD CHECKLIST

- ☐ MLH1, MSH2, MSH6, PMS2, EPCAM; AD; ~1 in 300.
- ☐ MutSα (MSH2/MSH6), MutLα (MLH1/PMS2); MSI-H.
- ☐ Endometrial ≈ bowel risk; sentinel cancer; endometrioid/clear cell ovary.
- ☐ Universal IHC: all endometrial (DG42) and colorectal (DG27).
- ☐ MLH1 loss → promoter methylation; methylated = sporadic.
- ☐ Germline panel + MLPA; Lynch-like → tumour somatic testing.
- ☐ Colonoscopy 2-yearly: 25 (MLH1/MSH2), 35 (MSH6/PMS2).
- ☐ No gynae screening; TAH + BSO ~35–40; HRT to 51.
- ☐ Aspirin (NG151); H. pylori; immunotherapy for dMMR.
- ☐ Muir–Torre; CMMRD (biallelic); PGT-M.

Self-assessment — cover the right-hand column

Question	Answer
Commonest inherited cause of endometrial cancer?	Lynch syndrome
Which proteins pair with MLH1 and MSH2?	PMS2 and MSH6 respectively
Next test after MLH1/PMS2 loss on IHC?	MLH1 promoter methylation
Meaning of methylated MLH1 promoter?	Usually sporadic (not Lynch)
NICE guidance for endometrial MMR testing?	DG42 (2020)
Colonoscopy start for MLH1/MSH2 carriers?	Age 25, 2-yearly
Is annual TVUS + pipelle surveillance recommended?	No — no proven benefit
Risk-reducing surgery?	Hysterectomy + BSO from ~35–40
Drug that reduces bowel cancer in Lynch?	Aspirin
Why do dMMR cancers respond to PD-1 inhibitors?	High mutation/neo-antigen load

7 References

- NICE DG42. Testing strategies for Lynch syndrome in people with endometrial cancer. 2020; NICE DG27 (colorectal) 2017; NG151 (colorectal cancer) 2020.
- Crosbie EJ et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med 2019.
- Monahan KJ et al. Guidelines for the management of hereditary colorectal cancer (BSG/ACPGBI/UKCGG). Gut 2020.