PIPADOR REVISION

MRCOG Part 1 Revision Notes

Hereditary Breast and Ovarian Cancer

CELL BIOLOGY • LECTURE 123

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 123: Hereditary Breast and Ovarian Cancer (HBOC)

Cell biology • Visual revision edition — cancer genetics begins

COLOUR CODE USED THROUGHOUT THESE NOTES

BRCA1 / PATHOGENIC	BRCA2 / SCREENING	PARP / OTHER GENES	SAFE / REPRODUCTION	VUS / SURGERY

LEARNING OBJECTIVES — tick off as you go

- ☐ Explain BRCA function, two-hit inheritance and PARP synthetic lethality.
- ☐ Quote cancer risks for BRCA1 and BRCA2 carriers.
- ☐ Know who is tested in the NHS and how to interpret results.
- ☐ Plan surveillance and risk-reducing surgery by age and gene.
- ☐ Counsel on other HBOC genes, reproduction and pregnancy.

1 Genetics and PARP Inhibitors

IN ONE LINE: *BRCA1 (17q21) and BRCA2 (13q12) repair double-strand breaks by homologous recombination. Carriers inherit one faulty copy (AD, 50%); tumours lose the other. That same weakness makes them vulnerable to PARP inhibitors.*

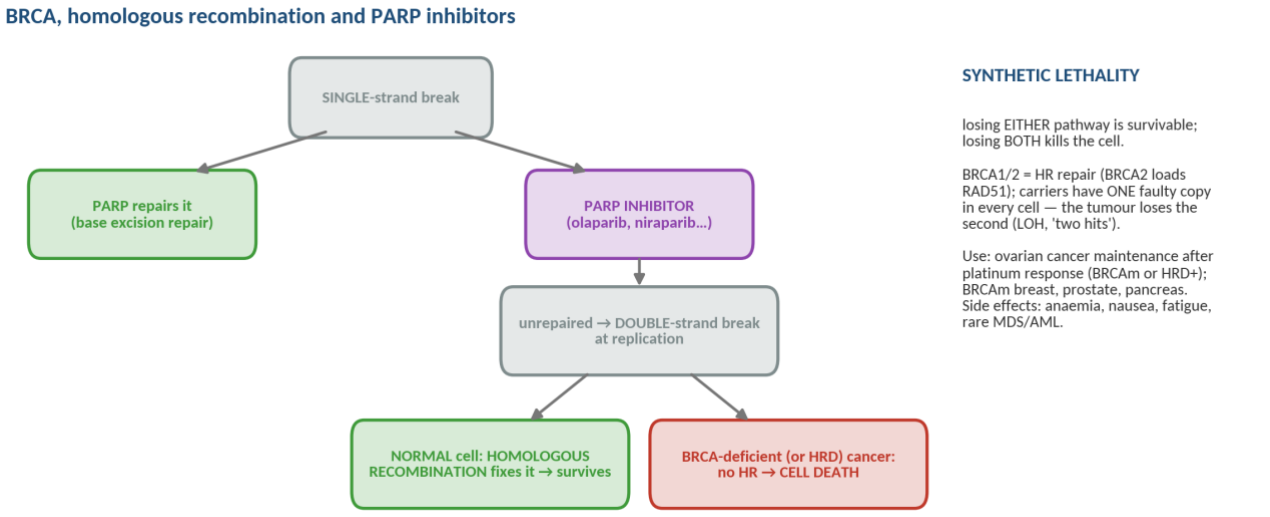
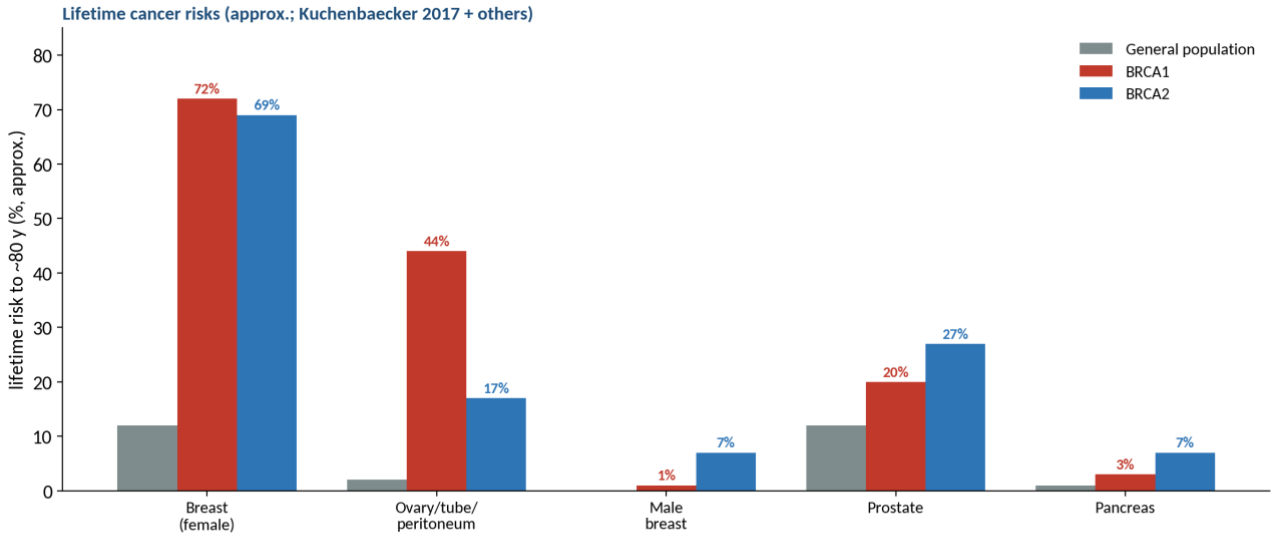


Figure 1. HR repair and synthetic lethality.

- **Frequency**: ~1 in 300–400 overall; ~1 in 40 Ashkenazi Jews carry one of three founder variants (BRCA1 c.68_69del [185delAG], c.5266dup [5382insC]; BRCA2 c.5946del [6174delT]).

2 Cancer Risks



BRCA1: triple-negative breast cancer, ovarian cancer earlier (from ~40). BRCA2: ER+ breast, ovarian later (from ~50), male breast, aggressive prostate, pancreas, melanoma.
Both: HIGH-GRADE SEROUS tubo-ovarian cancer — many start in the fallopian-tube fimbria (STIC).

Figure 2. Lifetime cancer risks.

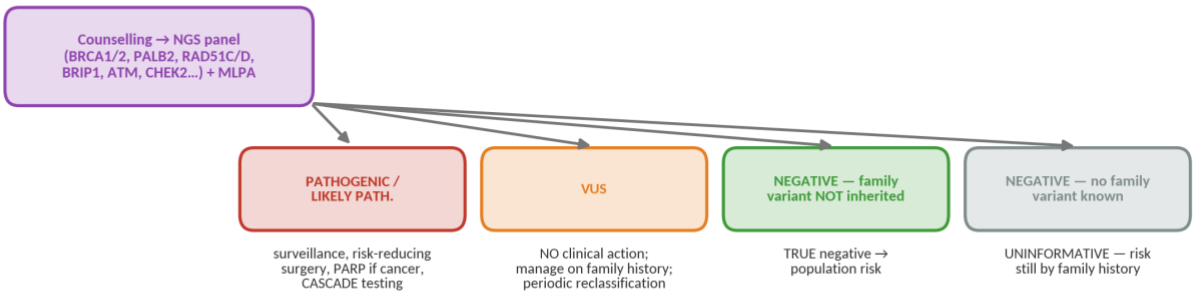
MNEMONIC / MEMORY HOOK

'BRCA1 = Breast + ovary, Early, triple-negative; BRCA2 = BRother's breast + prostate + pancreas, later ovary'.

3 Testing

WHO GETS TESTED (NHS Test Directory; ≥ 10% carrier probability)

- ALL non-mucinous epithelial ovarian / tubal / peritoneal cancers (tumour ± germline) — 'mainstreamed'
- breast cancer: triple-negative < 60, bilateral, male, < 40, Jewish ancestry, or high Manchester/CanRisk score
- unaffected relatives of a known carrier (PREDICTIVE testing from 18)
- Jewish ancestry — NHS founder-variant testing programme (3 variants, ~1 in 40 carry)



Genetic data + insurance (UK Code): insurers cannot ask for PREDICTIVE results (only Huntington's for life cover > £500k).

Figure 3. Testing pathway and results.

4 Surveillance and Risk Reduction

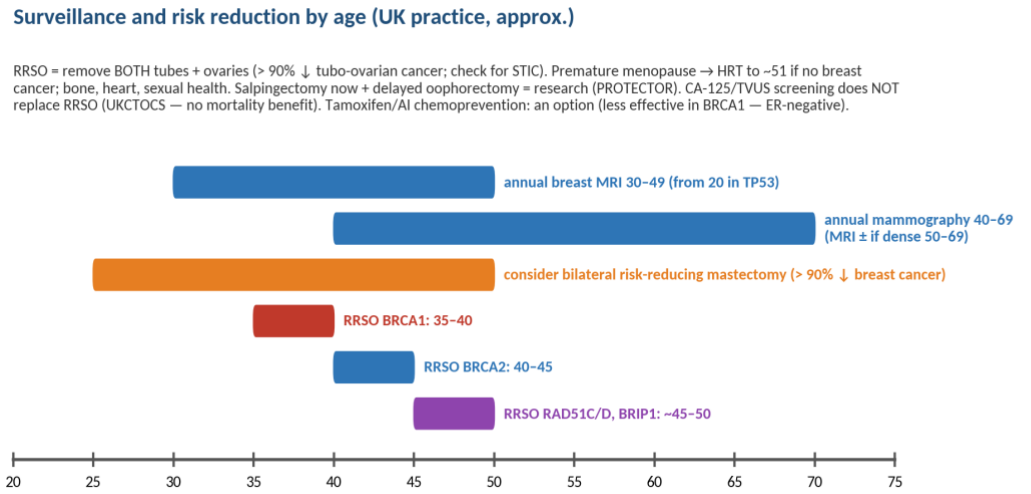


Figure 4. Surveillance and surgery by age.

- **STIC** (serous tubal intraepithelial carcinoma) in an RRSO specimen → gynae-oncology MDT; consider staging; long-term risk of later peritoneal cancer.

5 Other Genes, Reproduction and Pregnancy

Other HBOC genes

PALB2	breast ~50%; ovary ~5%; pancreas	MRI like BRCA; consider RRBM; RRSO ~45–50
ATM / CHEK2	breast ~20–30% (moderate)	enhanced breast screening; no routine RRSO
RAD51C / RAD51D	ovary ~10–13%; breast ↑ (esp. TNBC)	RRSO ~45–50
BRIP1	ovary ~5–6%	RRSO ~45–50
TP53 (Li–Fraumeni)	very early breast, sarcoma, brain, adrenal, leukaemia	MRI from 20, avoid radiation; whole-body MRI
PTEN / STK11 / CDH1	Cowden / Peutz–Jeghers / lobular breast + diffuse gastric	syndrome-specific; STK11 → ovarian SCTAT, cervical adenoma malignum

REPRODUCTION + PREGNANCY

- plan family before RRSO (BRCA1 by ~35–40); egg/embryo freezing; PGT-M (HFEA-approved) or PND; 50% transmission; children tested only as adults
- pregnancy: pause screening; investigate any lump with ULTRASOUND (± mammography with shielding); avoid gadolinium; MRI screening may resume while breastfeeding • breastfeeding encouraged (modest protection) • pregnancy-associated breast cancer → MDT; surgery any trimester; chemo from 2nd

Figure 5. Other HBOC genes; reproduction and pregnancy.

★ PEARL

Test ALL non-mucinous epithelial ovarian cancers. RRSO (tubes + ovaries): BRCA1 at 35–40, BRCA2 at 40–45; HRT to ~51 if no breast cancer. CA-125/TVUS screening does not replace surgery.

VUS = no action. Negative test without a known family variant is UNINFORMATIVE. PARP inhibitors exploit synthetic lethality in BRCA/HRD cancers.

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

~72% / ~69% Breast: BRCA1 / BRCA2	**~44% / ~17%** Ovary: BRCA1 / BRCA2	**10%** Testing threshold	**1 in 40** Ashkenazi carriers
30–49 Annual breast MRI	**35–40 / 40–45** RRSO: BRCA1 / BRCA2	**> 90%** Risk reduction (RRSO, RRBM)	**~51** HRT until

HIGH-YIELD CHECKLIST

- ☐ BRCA1 17q21, BRCA2 13q12; HR repair; AD; two hits.
- ☐ Breast ~70%; ovary BRCA1 ~44%, BRCA2 ~17%; BRCA2: male breast, prostate, pancreas.
- ☐ Test all non-mucinous epithelial ovarian cancers; 10% threshold; Jewish founder programme.
- ☐ Panel + MLPA; P/LP actionable; VUS no action; uninformative negatives.
- ☐ MRI 30–49; mammography 40–69; TP53 MRI from 20.
- ☐ RRSO BRCA1 35–40, BRCA2 40–45, moderate genes ~45–50; HRT to 51.
- ☐ RRBM > 90% reduction; salpingectomy-first = research.
- ☐ UKCTOCS: screening no mortality benefit.
- ☐ PARP: synthetic lethality; olaparib, niraparib; maintenance after platinum.
- ☐ PGT-M; plan family before RRSO; pregnancy lumps → ultrasound.

Self-assessment — cover the right-hand column

Question	Answer
DNA repair pathway of BRCA1/2?	Homologous recombination
Lifetime ovarian cancer risk, BRCA1?	~40–45%
Which ovarian cancers get universal testing?	All non-mucinous epithelial
Recommended RRSO age for BRCA1?	35–40 (family complete)
Recommended RRSO age for BRCA2?	40–45
Why remove the tubes?	Many HGSC arise in the fimbria (STIC)
Does CA-125 + TVUS screening reduce mortality?	No (UKCTOCS)
Mechanism of PARP inhibitors?	Synthetic lethality with HR deficiency
Action for a VUS?	None — manage on family history; reclassify later
Breast lump in a pregnant carrier — first test?	Ultrasound

7 References

- NICE CG164. Familial breast cancer: classification, care and managing breast cancer and related risks. 2013 (updated 2023).
- Kuchenbaecker KB et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017.
- Hanson H et al. UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in RAD51C, RAD51D, BRIP1 and PALB2. J Med Genet 2023.