PIPADOR REVISION

MRCOG Part 1 Revision Notes

Autosomal Dominant Disorders

GENETICS • LECTURE 82

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 82: Autosomal Dominant Disorders

Genetics • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

CANCER / RISK	LOSS OF FUNCTION	DOMINANT NEGATIVE / NEURO	GAIN OF FUNCTION / CARDIAC	MANAGEMENT

LEARNING OBJECTIVES — tick off as you go

- ☐ Recognise AD inheritance and explain the three mechanisms of dominance.
- ☐ Know the common AD conditions by system.
- ☐ Manage BRCA carriers and Lynch syndrome in gynaecology.
- ☐ Explain anticipation, de novo mutations and the paternal age effect.
- ☐ Counsel on predictive testing, reproduction and pregnancy (Marfan, myotonic dystrophy, ADPKD).

1 Features and Mechanisms

IN ONE LINE: *One faulty copy is enough: every generation, both sexes, male-to-male transmission, 50% risk to each child — modified by penetrance, expressivity and new mutations.*

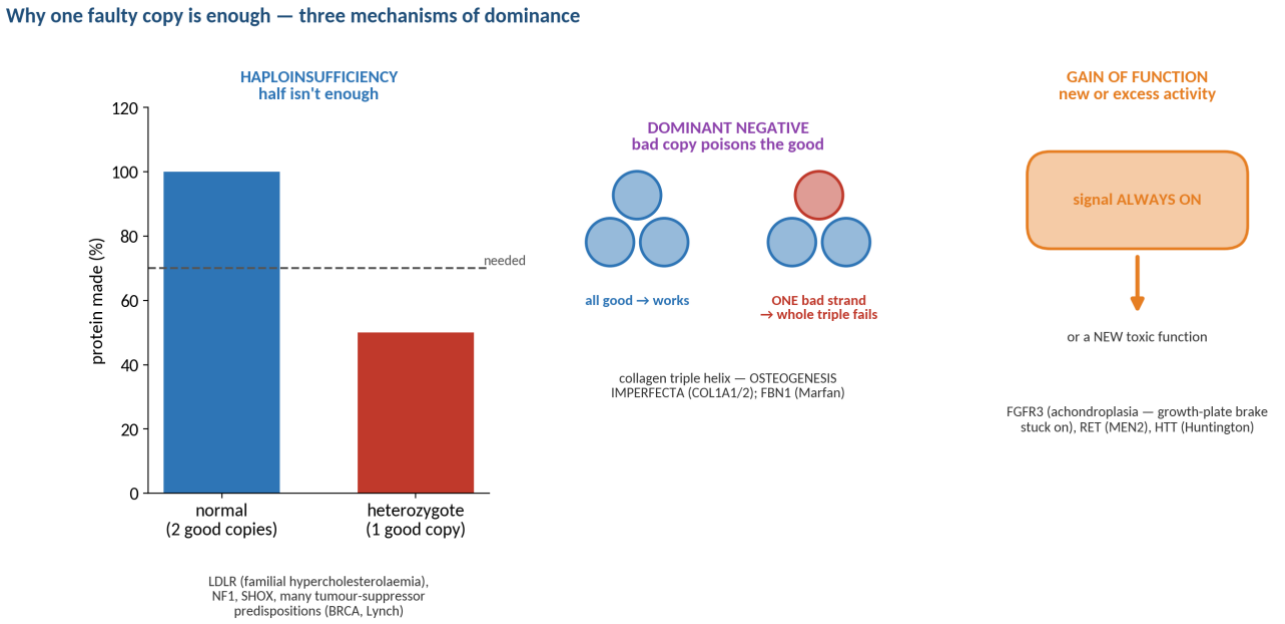


Figure 1. Haploinsufficiency, dominant negative, gain of function.

- Marfan (FBN1) is classically **dominant negative** (abnormal fibrillin disrupts microfibrils), though some variants act by haploinsufficiency. Cancer-predisposition genes are **inherited** dominantly but act **recessively in the cell** — the second copy is lost in the tumour (Knudson's two hits).

2 Common AD Conditions

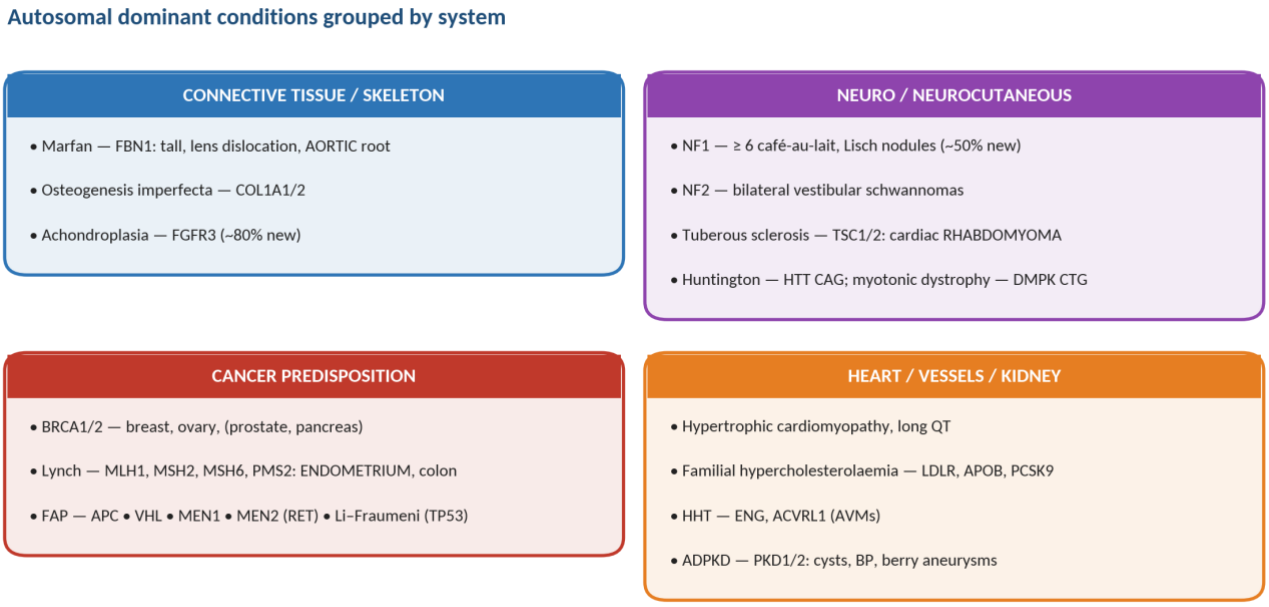


Figure 2. AD conditions by system.

3 Hereditary Breast and Ovarian Cancer

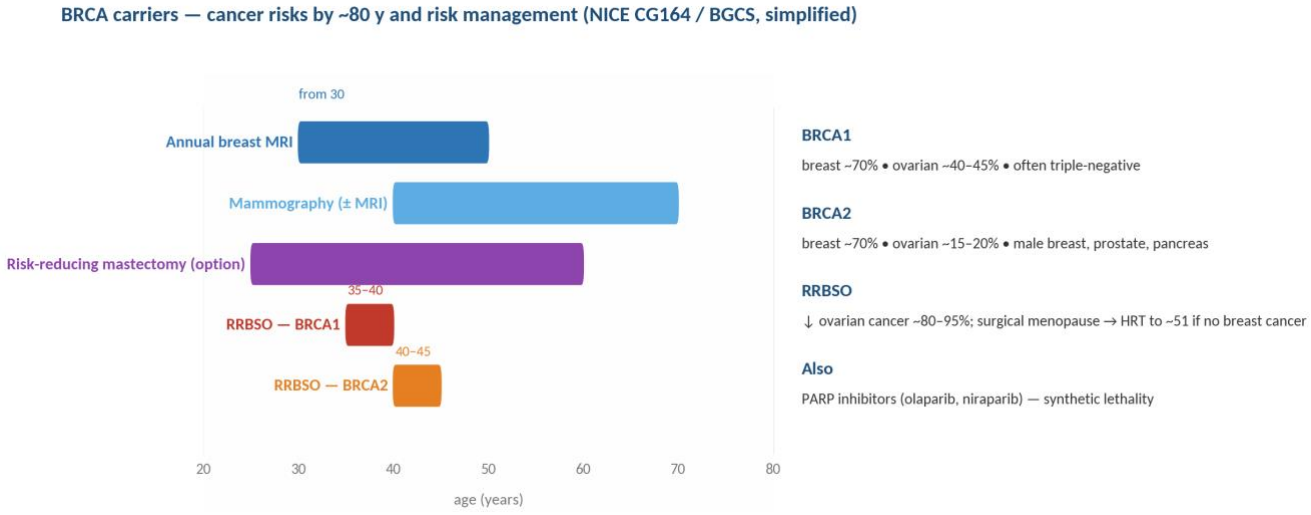


Figure 3. BRCA risk management.

Topic	Key points
Biology	Homologous-recombination DNA repair; tumours vulnerable to PARP inhibitors (synthetic lethality)
Who to test	Strong family history (NICE CG164 criteria), Ashkenazi Jewish ancestry (founder variants), all women with non-mucinous epithelial ovarian cancer, young / triple-negative breast cancer
Breast	Annual MRI 30–49; mammography from 40; risk-reducing mastectomy; chemoprevention (tamoxifen/anastrozole — limited benefit in BRCA1)

Topic	Key points
Ovary/tube	No effective screening → RRBSO BRCA1 ~35–40, BRCA2 ~40–45; most 'ovarian' cancers start in the fallopian tube (STIC). Salpingectomy with delayed oophorectomy only within research
After RRBSO	HRT to ~51 if no personal breast cancer; bone + heart health

4 Lynch Syndrome

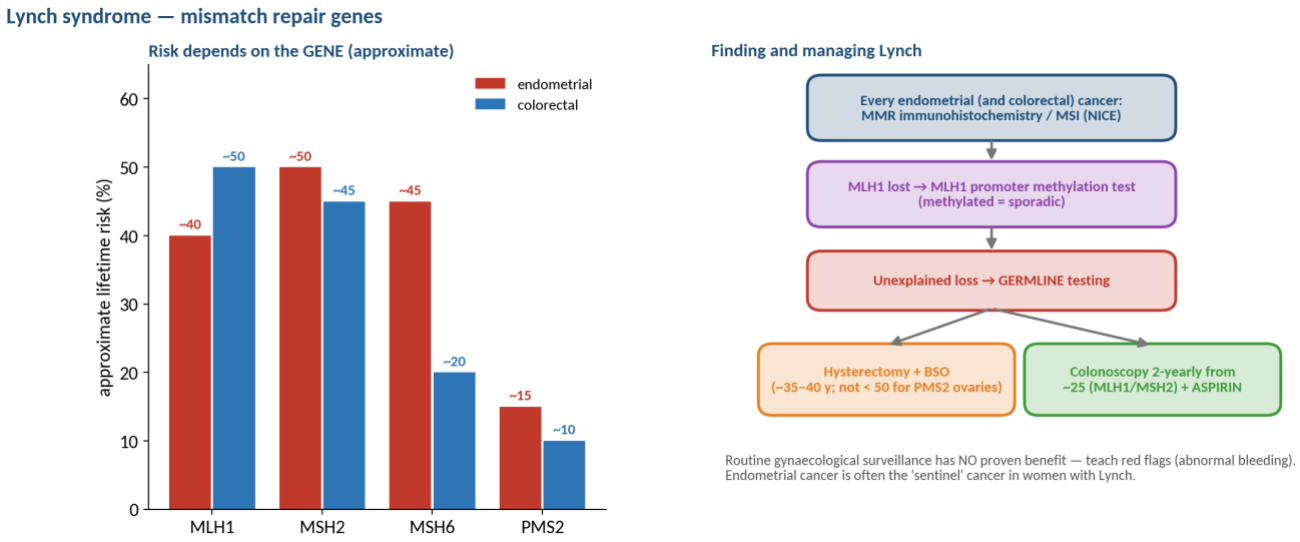


Figure 4. Lynch risks and pathway.

- Mismatch-repair genes; ~1 in 300 people. Endometrial and colorectal risks depend on the gene (MLH1/MSH2 highest, PMS2 lowest); also ovary, stomach, urinary tract, small bowel, brain, skin. Amsterdam II / revised Bethesda for clinical suspicion; **NICE DG42: test all endometrial cancers for MMR deficiency**.

> **MNEMONIC / MEMORY HOOK**
>
> **'BRCA = Breast + Ovary; Lynch = Lining (endometrium) + Large bowel.'**

5 Anticipation and New Mutations

Condition	Key points
Huntington (HTT CAG)	≤ 26 normal; 27–35 intermediate; 36–39 reduced penetrance; ≥ 40 full — expands mainly through fathers (juvenile HD)
Myotonic dystrophy (DMPK CTG)	Cataracts, myotonia, cardiac conduction, diabetes; congenital form through affected MOTHERS — polyhydramnios, reduced movements, neonatal hypotonia/respiratory failure; uterine inertia + PPH
Spinocerebellar ataxias	CAG repeats; (Friedreich ataxia is AR — GAA)
Paternal age effect	Achondroplasia (~80% new), Apert/Crouzon/Pfeiffer (FGFR2) — ↑ new mutations in older fathers' sperm

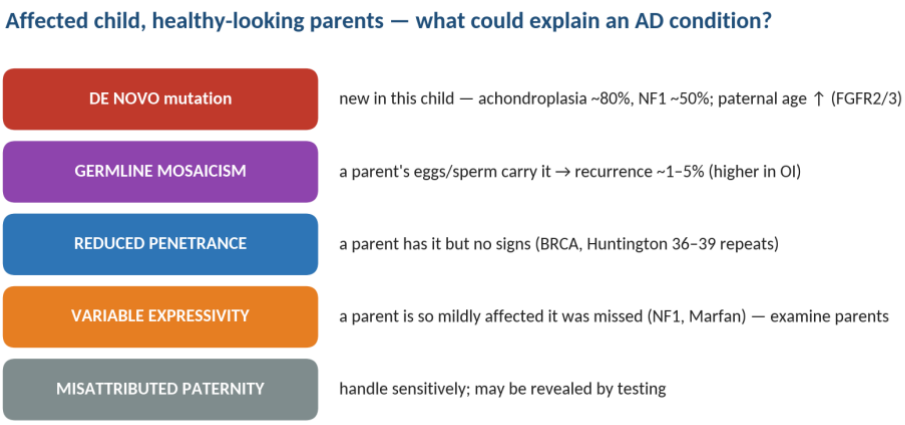


Figure 5. Apparently sporadic AD cases.

6 Counselling and Pregnancy

PREDICTIVE TESTING

- Late-onset conditions (Huntington, BRCA, Lynch): pre-test + post-test counselling, time to decide
- **Don't test children** for adult-onset conditions unless it changes care in childhood (e.g. FAP, MEN2)
- UK insurance Code: predictive results can only be asked for **Huntington's + life cover > £500,000**

REPRODUCTION

- 50% per pregnancy for an affected parent
- **PGT-M** (BRCA, HD — including exclusion testing), CVS/amnio, donor gametes
- NIPD (cfDNA) for FGFR3 conditions and paternally inherited variants

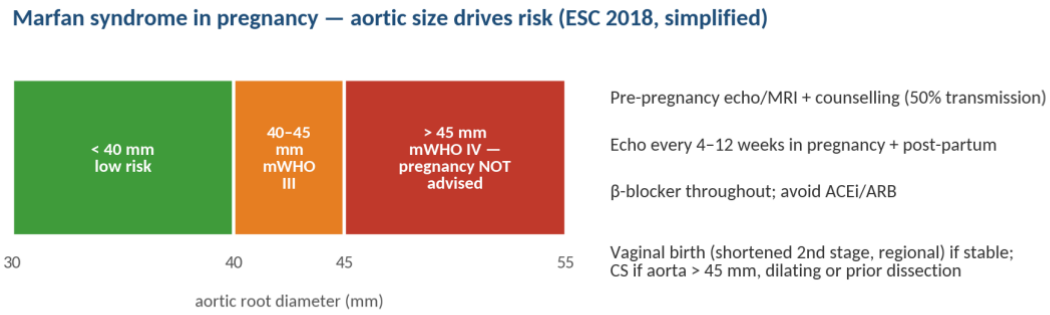


Figure 6. Marfan and pregnancy.

- **ADPKD**: hypertension and **pre-eclampsia** more common; check renal function and BP; screen for intracranial aneurysm if family history. **NF1**: hypertension (consider phaeochromocytoma, renal artery stenosis), neurofibromas may grow in pregnancy.

★ **PEARL**

RRBSO: BRCA1 ~35–40, BRCA2 ~40–45; Lynch hysterectomy + BSO ~35–40 after childbearing. Routine ovarian or endometrial screening does not work — surgery does.

Huntington expands through fathers; congenital myotonic dystrophy comes from mothers.

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Numbers to know

50% Risk to each child	**~70%** BRCA breast risk	**~40–45% / ~15–20%** Ovarian: BRCA1 / 2	**35–40 / 40–45** RRBSO age BRCA1 / 2
30–49 Annual MRI	**~1 in 300** Lynch carriers	**≥ 40** HD CAG full penetrance	**> 45 mm** Marfan aorta — avoid pregnancy

HIGH-YIELD CHECKLIST

- ☐ AD: vertical, both sexes, male-to-male, 50%.
- ☐ Haploinsufficiency (LDLR), dominant negative (COL1A1, FBN1), gain of function (FGFR3, RET, HTT).
- ☐ Tumour-suppressor genes: dominant inheritance, two-hit mechanism.
- ☐ BRCA: MRI 30–49, RRBSO 35–40 / 40–45, PARP inhibitors.
- ☐ Lynch: MMR genes; test all endometrial cancers; hysterectomy + BSO; aspirin.
- ☐ Anticipation: HD (paternal), myotonic dystrophy (congenital = maternal).
- ☐ Paternal age: achondroplasia, FGFR2 craniosynostoses.
- ☐ Sporadic case: de novo, mosaicism, penetrance, expressivity, paternity.
- ☐ Predictive testing rules; no testing of children for adult-onset disease.
- ☐ Marfan: aorta > 45 mm = pregnancy not advised; β-blocker; ADPKD → pre-eclampsia.

Self-assessment — cover the right-hand column

Question	Answer
Feature that rules out X-linked inheritance?	Male-to-male transmission
Mechanism in osteogenesis imperfecta?	Dominant negative (collagen)
Mechanism in achondroplasia?	Gain of function (FGFR3)
Age for RRBSO in BRCA1 carriers?	~35–40
Why do PARP inhibitors work in BRCA cancers?	Synthetic lethality — no back-up DNA repair
Commonest cancer in women with Lynch?	Endometrial (gene-dependent)
First test on an endometrial cancer for Lynch?	MMR immunohistochemistry / MSI
Parent through whom HD tends to expand?	Father
Parent who passes congenital myotonic dystrophy?	Mother
Marfan aortic root at which pregnancy is not advised?	> 45 mm

8 References

- NICE CG164. Familial breast cancer. 2013 (updated 2023).
- NICE DG42. Testing strategies for Lynch syndrome in people with endometrial cancer. 2020.
- BGCS. Recommendations for gynaecological cancer risk management in BRCA / Lynch carriers.
- Regitz-Zagrosek V et al. 2018 ESC Guidelines — cardiovascular disease in pregnancy.