Mutations

Disease/Disorder	Genes mutations
Testes germ cells tumours	- Extra copies of the short arm of chromosome 12, usually due to the presence of an isochromosome 12 [i(12p), a chromosome with two copies of the short arm (12p) and no long arm], are found in postpubertal germ cell tumors and germ cell neoplasia in situ, but not in spermatocytic seminoma. Oncogenic mutations in KIT which are found in up to 25% of tumours.
Prostate adencarcinoma	- Germline mutations in hereditary prostate cancer (younger age presentation) like BRCA 1 & 2, and HOXB13. - Acquired somatic mutations: Most common somatic genomic rearrangement is fusion of the androgen regulated gene TMPRSS2 with a member of the ETS transcription factor family (**ERG**, ETV1, ETV4 and FLI1), TMPRSS2 genes----ETS fusion 50% of prostate cancer. - Numerous single nucleotide polymorphisms (SNPs) that have a low to moderate effect on risk / progression have been identified.
Endometriosis	Endometriosis in patients without cancer harbors oncogenic mutations in ARID1A (mc/ tumor suppressor gene).
Endometrial hyperplasia	Inactivation of the PTEN tumor suppressor gene has been identified at a substantial frequency in hyperplasia with atypia (approximately **50**%) and endometrioid carcinoma (>**70**%).
Endometrial carcinoma	- Mutations (inactivation) in mismatch repair genes (MMR deficient) and the tumor suppressor gene PTEN are early events in the stepwise development of endometrioid carcinoma. - TP53 mutations occur but are relatively uncommon and are late events in the genesis of this tumor type. - **POLE** gene mutation : better prognosis - Women with germline mutations in **PTEN** (Cowden Syndrome) (In GI hamartoma multiple GI polyps). - Germline alterations in DNA **mismatch repair genes** (Lynch Syndrome) (Right sided colon cancer) are at high risk for this cancer.
Endometrial Serous cancers	- Nearly all cases of serous carcinoma have mutations in the TP53 tumor suppressor gene. - Whereas mutations in DNA mismatch repair genes and in PTEN are rare/late.
Endometrial polyps	The stromal cells are monoclonal, often with a rearrangement of chromosomal region 6p21, and thus constitute the neoplastic component of the polyp.
Leiomyoma	- Chromosomal abnormalities: e.g. rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas. - Mutations in the MED12 gene, which encodes a component of the RNA polymerase transcription complex, have been identified in up to **70**% of leiomyomas.
HPV (+) VIN	HPV oncoproteins E6 and E7 inhibit p53 and RB (tumour supressor genes)---resulting in the overexpression of p16 (+ by IHC).
HPV (-) VIN	HPV unrelated precancerous lesions (HPV-, atypia in basal cell layer), Somatic mutation: like p53 mutations.
PCOS	Familial clustering of cases has been observed, strongly suggesting a genetic basis for polycystic ovary disease, however, no specific genetic abnormality has been shown to be the sole culprit in the development of polycystic ovary disease.
Mucinous ovarian carinoma	Mutations in **KRAS** are detected in approximately **50%** of ovarian mucinous carcinomas
Serous ovarian carcinoma	- Low grade serous: Mutations in genes encoding signaling proteins: **KRAS** **and BRAF mutation in 50-60%**, **NRAS** mutation (**KBN**) - High grade serous: **TP53** mutations in nearly all cases Germline, somatic or promoter hypermethylation (inactivation) of **BRCA1 and BRCA2 in 50%** of cases Women with tumours containing **BRCA1/2** mutations tend to have a better prognosis than women whose tumours lack these genetic abnormalities
Endometrioid ovarian carcinoma	- **CTNNB1** (**53%**)--- WNT/beta catenin - **KRAS** (**33%**)

Disease/Disorder	Syndromes/DDx
Endometrial carcinoma	- (Cowden Syndrome): (GI hamartoma & multiple GI polyps) (germline mutations in PTEN) - (Lynch Syndrome): (Right sided colon cancer) (germline mutations in MMR)
Breast cancer	- (Cowden Syndrome): (GI hamartoma & multiple GI) (germline mutations in PTEN) - Li-Fraumeni syndrome (germline mutations in P53)
Mucinous ovarian carcinoma	- Krukenburg tumour: (Gastric cancer, signet ring mucins secreting cells) - Metastatic from the appendix
Ovarian carcinomas (KRAS mutations)	- GIT tumours
Cryptorchidism	- A small subset of the 10% of the cases (bilateral) are associated with many chromosomal abnormalities including: 1. Klinefelter syndrome (47, XXY), 2. Prader-Willi syndrome, 3. Testicular dysgenesis syndrome
Risk of germ cell neoplasia in situ	- Disorders of sex development (androgen insensitivity syndrome and testicular dysgenesis)