Endometrial cancer

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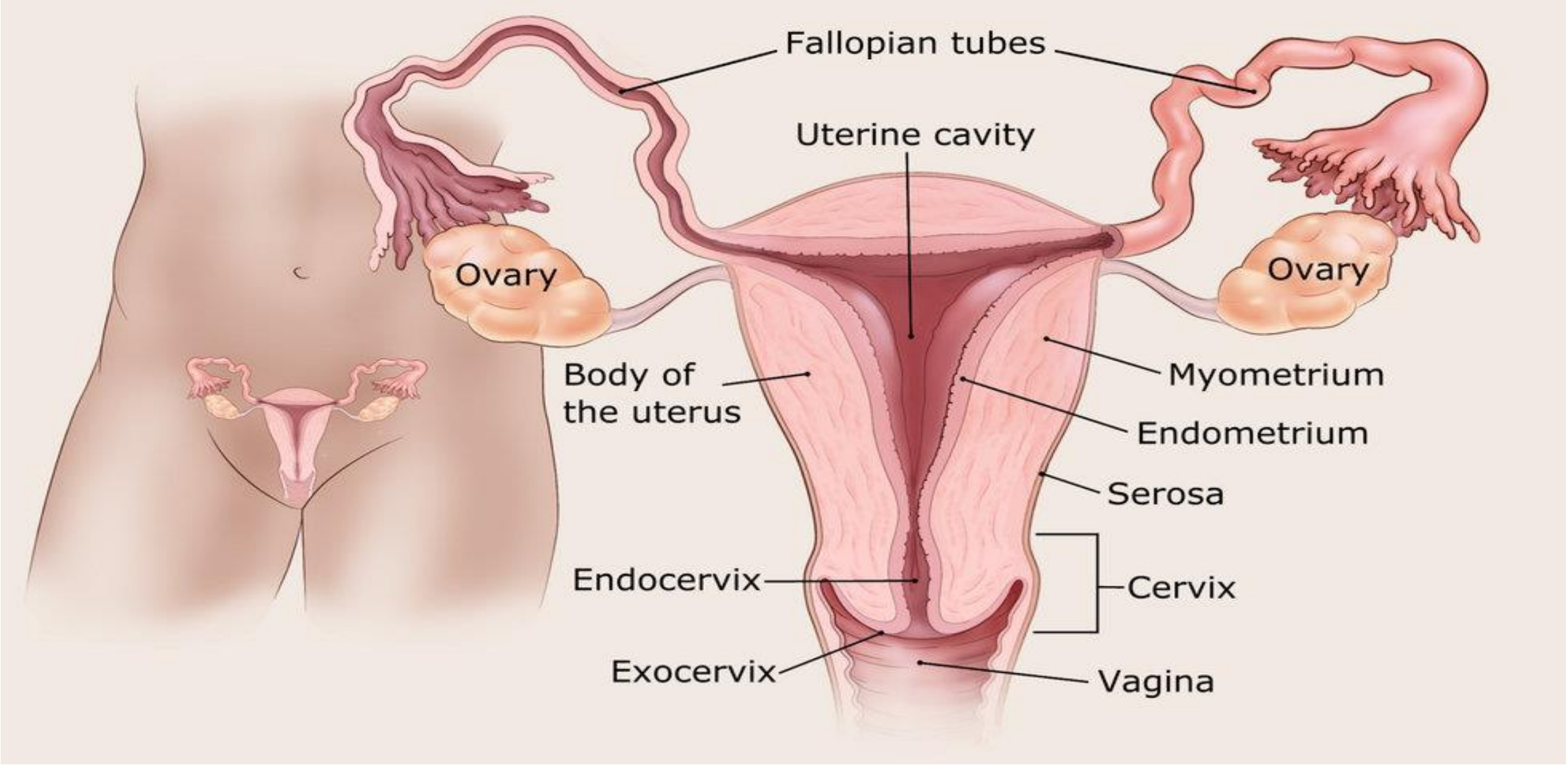
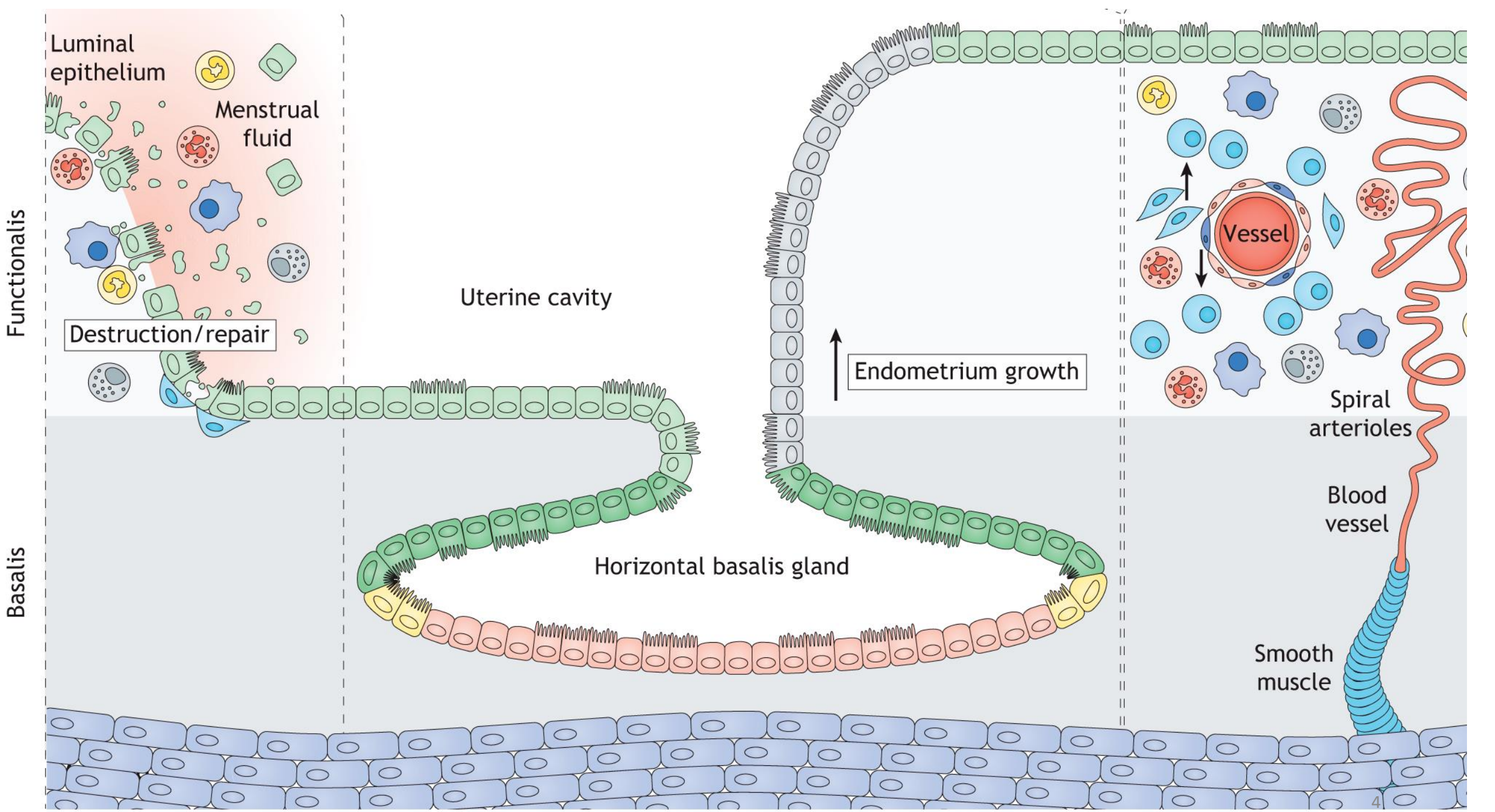
Basic uterine Anatomy

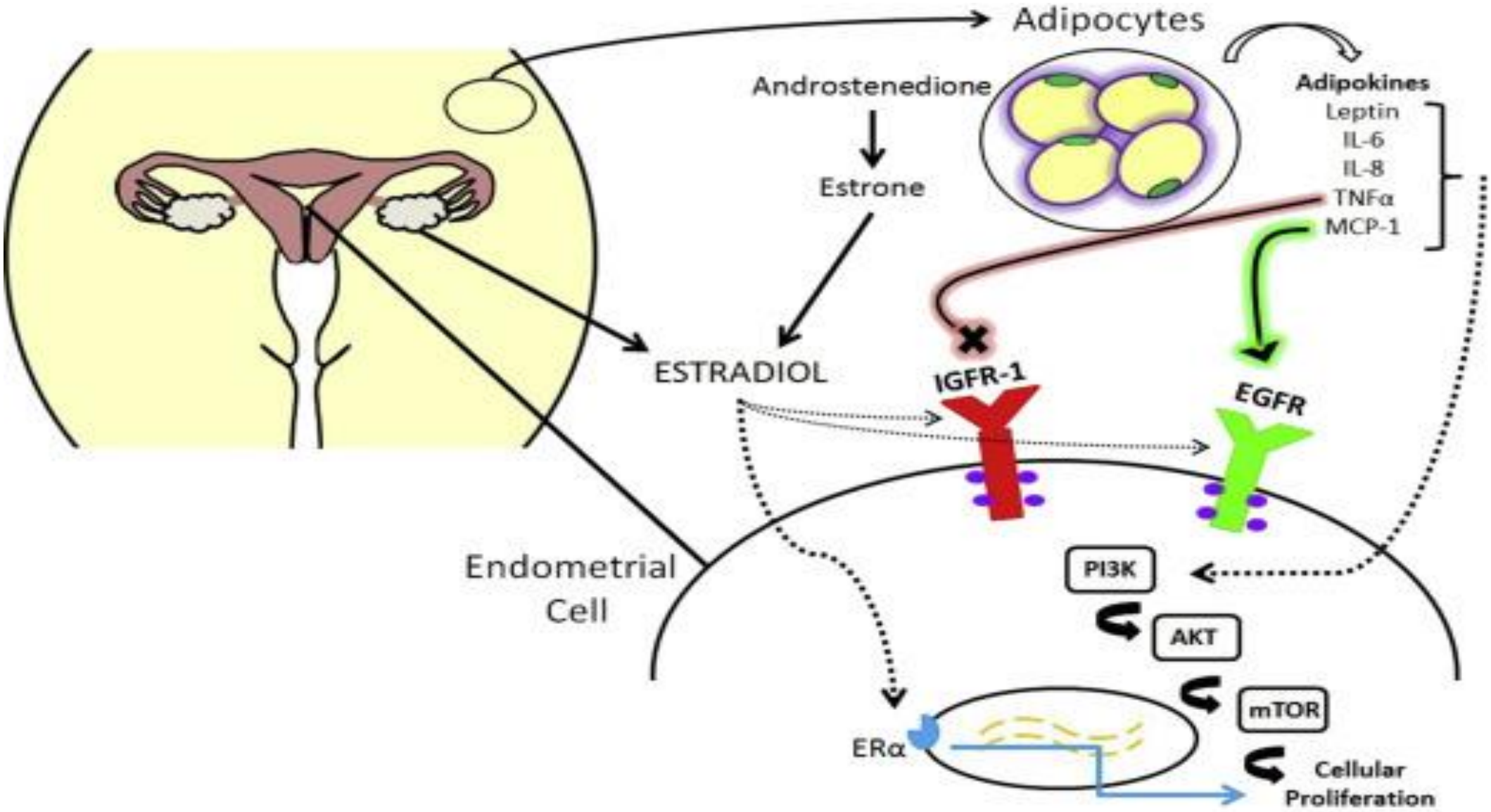


The endometrium

- A multicellular tissue forming the lining of the uterus.
- The function of the endometrium is to either;
    - prepare for embryonic implantation and maintain a pregnancy or,
    - In the absence of pregnancy, to shed and repair, that is, menstruate.
- Comprises two layers,
    1. The outer functionalis (functional) and the
    2. Underlying basalis (basal) layer proximal to the myometrium


Luminal epithelium
Menstrual fluid
Functionalis
Uterine cavity
Destruction/repair
Endometrium growth
Vessel
Spiral arterioles
Blood vessel
Basalis
Horizontal basalis gland
Smooth muscle

Role of Estrogen



How do cancers develop?

- Cancers are caused by changes to genes (genetic changes) that control the way our cells function, especially how they grow and divide.
- Genetic changes include;
    1. Errors as cells divide
    2. DNA damage related to teratogens (environmental exposures e.g. smoking, drugs etc)
    3. Inherited genetic defects from parents
- Failure of the body to eliminate these abnormal genetic changes leads to cancerous development. This increases with age (wear and tear)

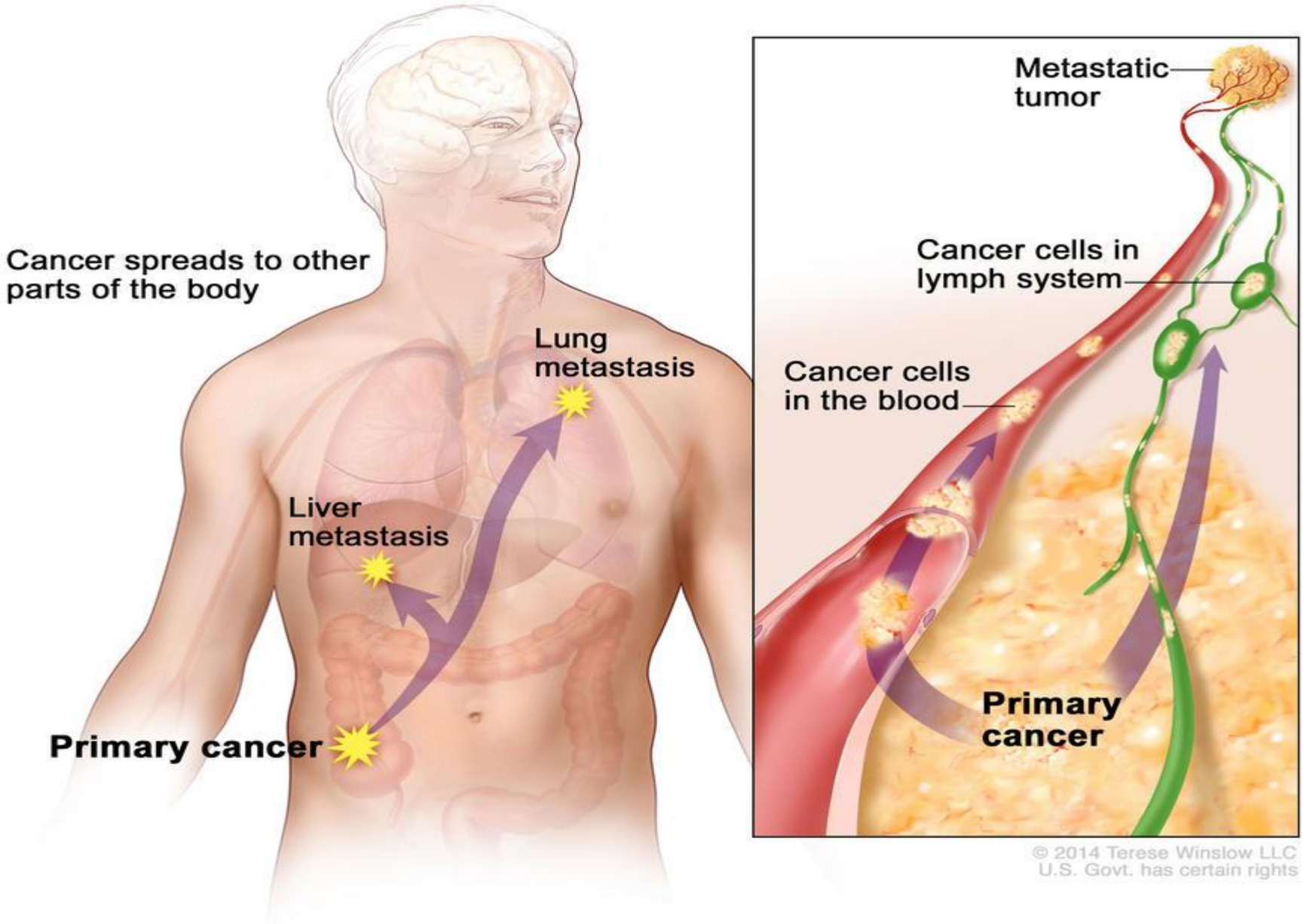
What makes Cancer cells different from normal cells

1. Grow uncontrollably
2. Ability to spread to other parts of the body (normal cells stop to grow when they encounter neighbouring cells)
3. Ability to grow in the absence of signals telling them to grow (unlike normal cells)
4. Ability to Ignore signals that normally tell cells to stop dividing or to die (programmed cell death or Apoptosis)
5. Ability to tell blood vessels to grow toward tumours.

Genes that lead to cancers

1. Proto-oncogenes (responsible for normal cell growth and division)
    - When altered, the become Oncogenes hence allowing cells to grow and survive when they should not
2. Tumour suppressor genes (Control cell growth and division)
    - When altered cells divide uncontrolled division
3. DNA repair genes (involved in fixing damaged DNA)

Metastasis


Cancer spreads to other parts of the body
Lung metastasis
Liver metastasis
Primary cancer
Metastatic tumor
Cancer cells in lymph system
Cancer cells in the blood
Primary cancer
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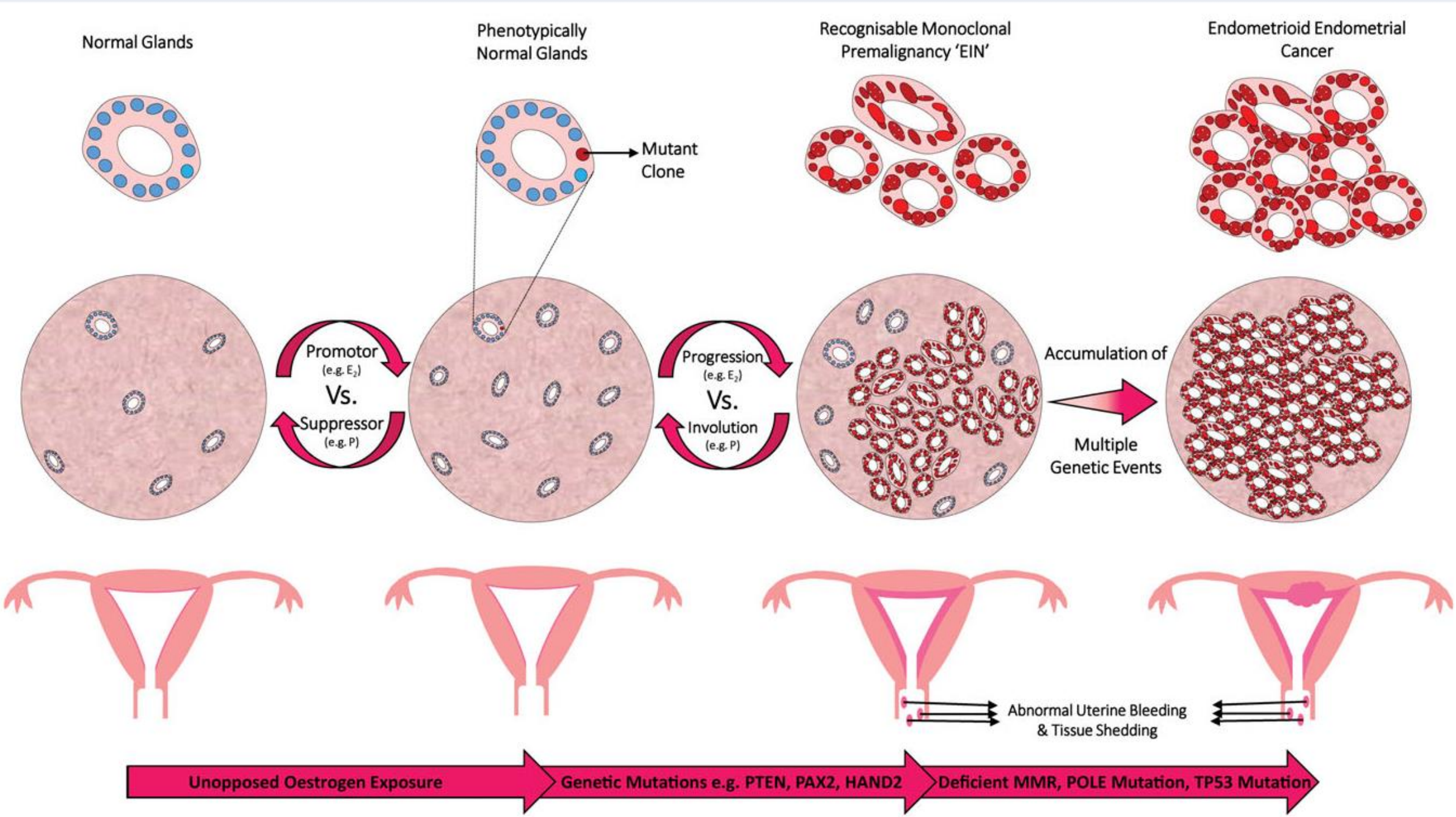
Endometrial cancer and its pathophysiology

- Also called endometrial carcinoma or Uterine cancer
- A carcinoma is a cancer formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body


Normal Glands
Phenotypically Normal Glands
Recognisable Monoclonal Premalignancy 'EIN'
Endometrioid Endometrial Cancer
Mutant Clone
Promotor (e.g. E_2)
Vs.
Suppressor (e.g. P)
Progression (e.g. E_2)
Vs.
Involution (e.g. P)
Accumulation of
Multiple Genetic Events
Abnormal Uterine Bleeding & Tissue Shedding
Unopposed Oestrogen Exposure
Genetic Mutations e.g. PTEN, PAX2, HAND2
Deficient MMR, POLE Mutation, TP53 Mutation

Endometrial Carcinoma: Stages at Presentation and 5-Year Survival Rates

Endometrioid		Papillary serous	
Present at earlier stage		**Present at more advanced stage**	
Stage I	73%	Stage I	54%
Stage II	11%	Stage II	8%
Stage III	13%	Stage III	22%
Stage IV	3%	Stage IV	16%
Survival Rates		**Survival Rates**	
Stage I	85%–90%	Stage I	60%
Stage II	70%	Stage II	50%
Stage III	40%–50%	Stage III	20%
Stage IV	15%–20%	Stage IV	5%–10%

Data from Dunton et al.[3]

Endometrial Carcinoma Subtypes

Histology	Number
Endometrioid	3,769 (87.4%)
Papillary serous	127 (2.9%)
Clear cell	94 (2.2%)
Mucinous	26 (0.6%)
Squamous cell	7 (0.2%)
Other	289 (6.7%)

Histological classification

- Based on WHO classification of tumors
- Adenocarcinoma (Endometrioid vs Non Endometrioid)
- Uterine Carcinosarcoma
- Squamous cell carcinoma
- Small cell carcinoma
- Transitional carcinoma
- Serous carcinoma

Histological Grading of Endometrial cancers

- The grade is based on how much the cancer cells are organized into glands that look like the glands found in a normal, healthy endometrium.
- Lower grade cancers (grades 1 and 2), more of the cancer cells form glands.
- **High grade cancers** (grade 3), more of the cancer cells are disorganized and do not form glands.
  - Grade 1: 95% or more of the cancer tissue forming glands.
  - Grade 2: 50% and 94% of the cancer tissue forming glands.
  - **Grade 3:** less than half of the cancer tissue forming glands. (aggressive, poorer prognosis)

Molecular profiling

- Based on the Cancer Genome Atlas (TCGA) i.e. from morphological to molecular classification.
- Four molecular subgroups characterized
    1. POLE mutation (POLEmut group), favourable prognosis
    2. Microsatellite instability (mismatch repair deficient [MMRd] group)
    3. high somatic copy-number alterations (serous-like group, driven by TP53 mutation, also called p53abn group), poor prognosis
    4. group without a specific driver mutation (NSMP group)

Risk factors for Endometrial cancer

- High/prolonged Estrogen exposure (with low progesterone levels) over a long time.
- Obesity (fat/cholesterol is a raw material for Estrogen-like compounds)
- Age > 50 years
- Early menarche (< 12 years)
- Late menopause (>52 years)
- Nulliparity (Pregnancy shifts balance to Progesterone)
- History of infertility
- Ovarian disease e.g.
    - Polycystic Ovarian Syndrome (x5 risk), Estrogen secreting Granulosa cell tumors

Risk factors continued

- DM (two times higher risk vs non diabetics)
- and Hypertension
- Family history of Endometrial Cancer
- Tamoxifen use for breast cancer (anti-estrogen in breast vs Estrogen effects in Uterus)
- History of Endometrial Hyperplasia
- Use of certain types of Hormone Replacement therapy (Estrogen only HRT)
- Genetic risk factors (lynch Syndrome i.e. HBOUC – Hereditary Breast Ovarian Uterine and Colon cancer syndrome)
- Use of COCs lowers risk of EC
- IUD use reduces risk

Symptoms

- Abnormal vaginal bleeding (>90%) if menopausal
- Intermenstrual bleeding (heavy bleeding between the periods), usually women in 30s and 40s

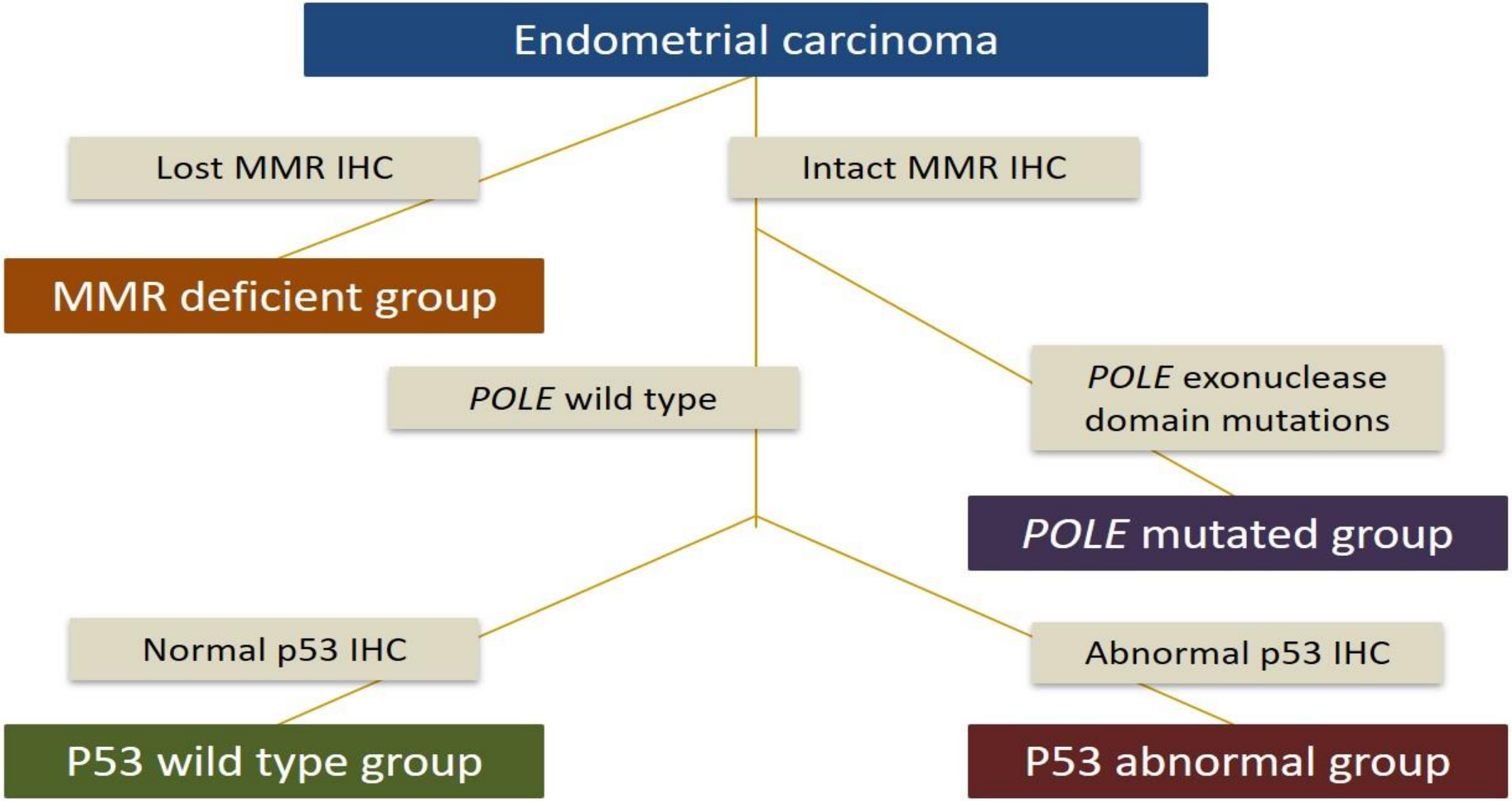
Pre-operative Diagnosis

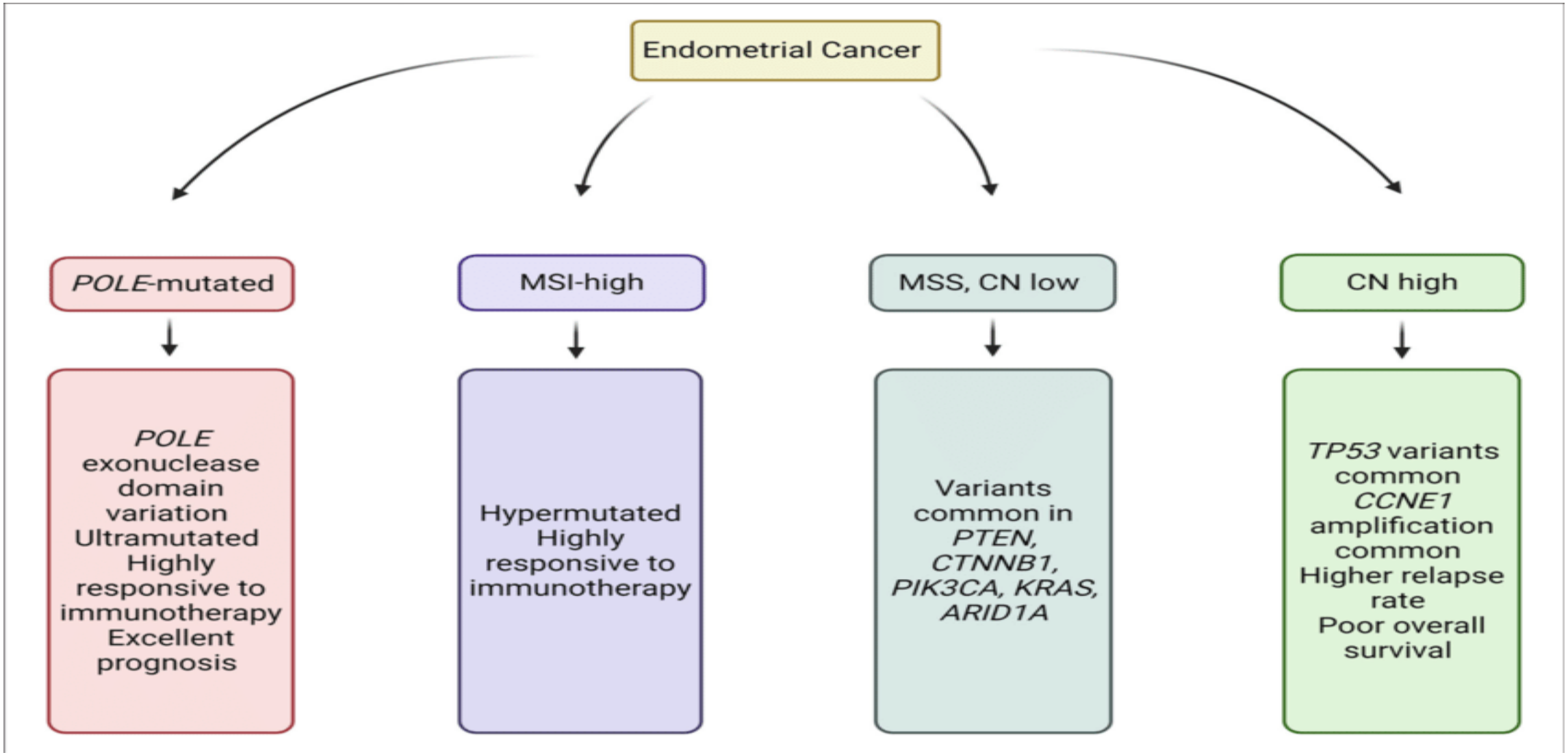
- Pelvic examination
- Transvaginal Ultrasound scan (Endometrial thickness <5mm)
- Endometrial biopsy (sample of tissue from the inner lining of the uterus)
    1. Pipelle aspiration biopsy
    2. Hysteroscopy guided biopsy
    3. D&C
- Histology report should note Tumor type and tumor grade
- MRI scanning to determine depth of myometrial invasion

Prognostic tumor characteristics

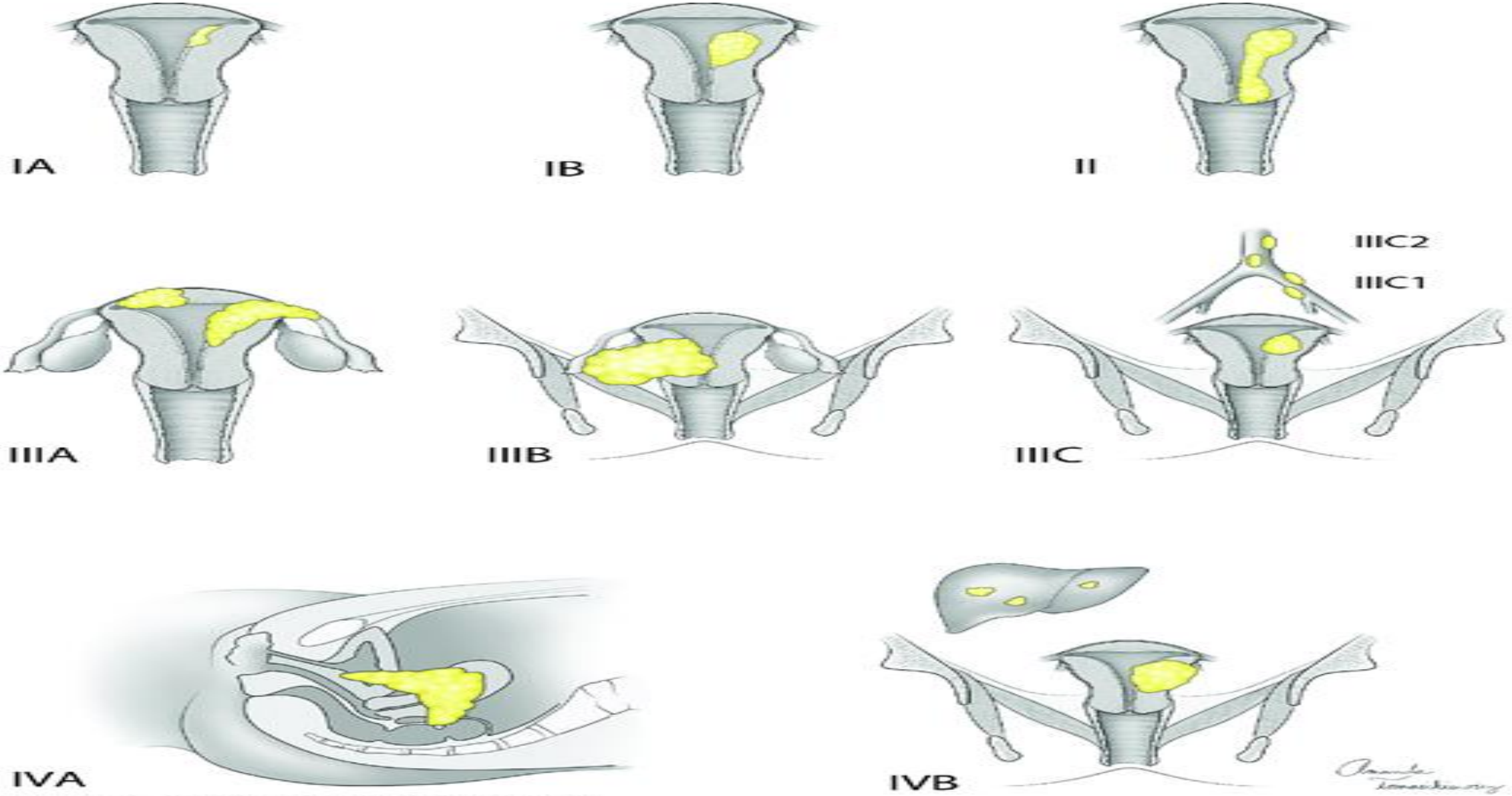
1. Tumor grade 3 (poorly differentiated)
2. LymphoVascular space invasion (especially substantial/extensive LVSI)
3. Non- Endometrioid histology (serous, clear cell, undifferentiated, small cell, carcinosarcoma)
4. Cervical stromal involvement.
5. Other molecular characteristics
    - P53 abnormal cancers have poor prognosis
    - POLE cancers have excellent prognosis

Molecular classification for EC prognosis

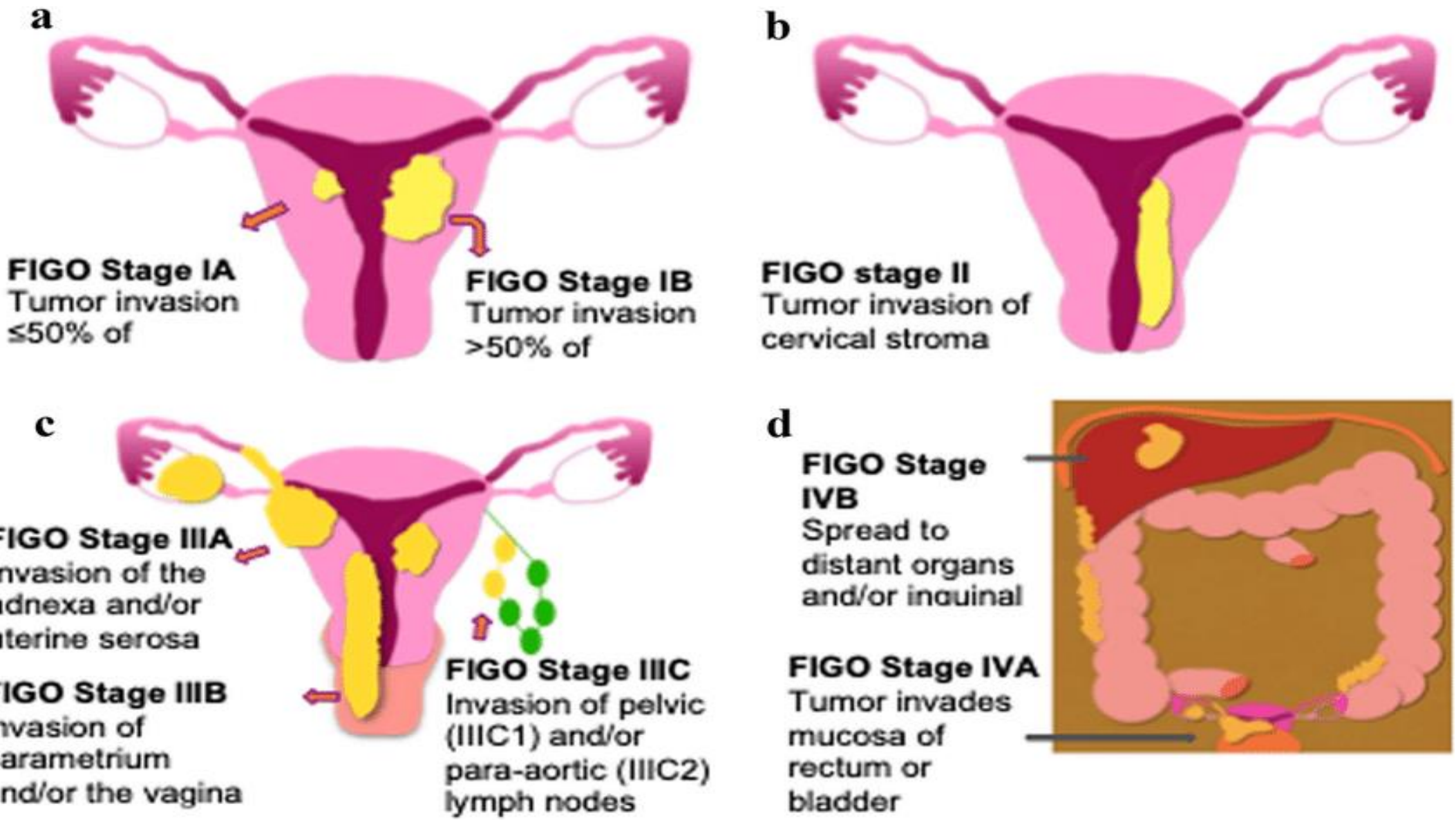


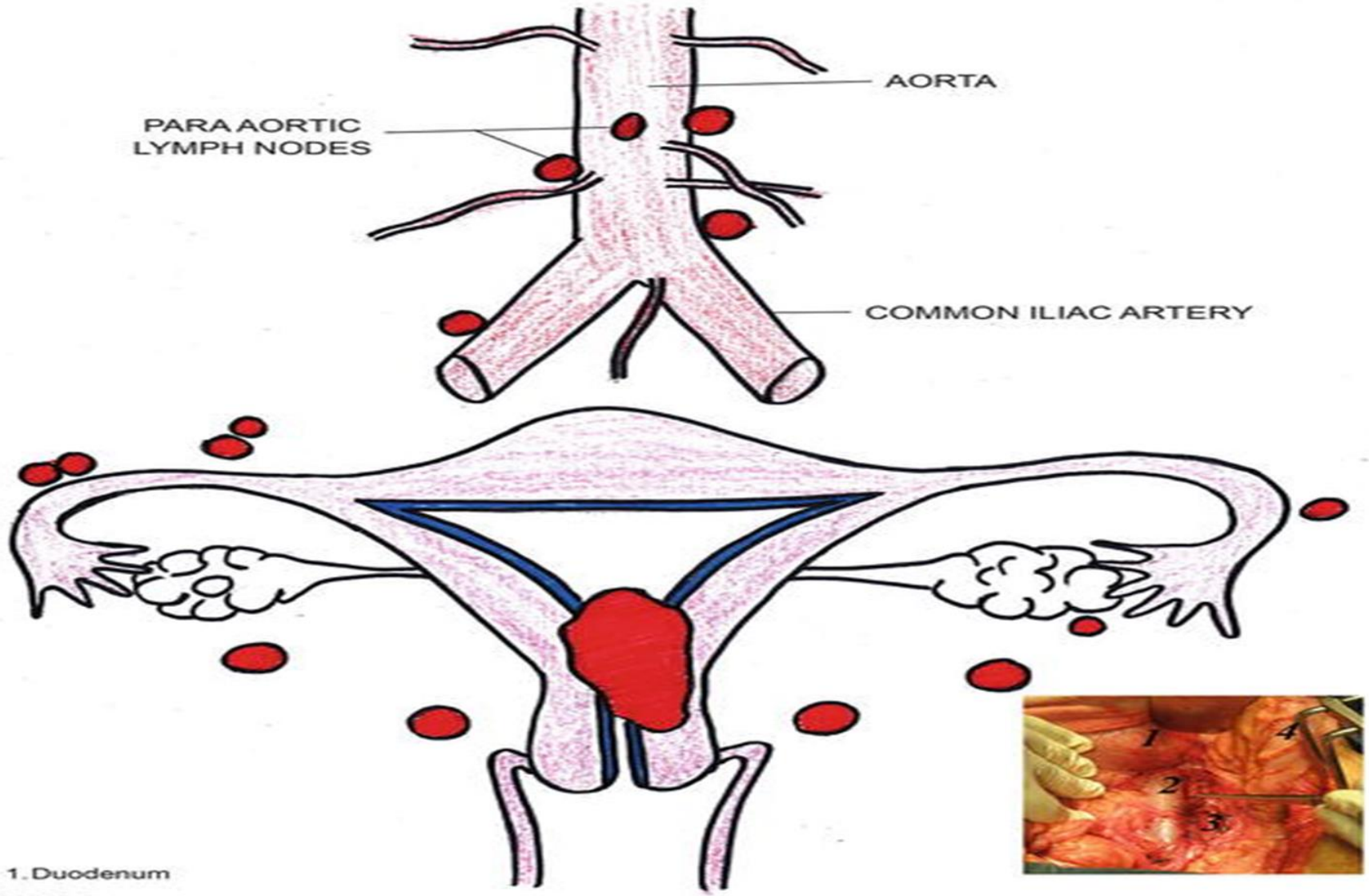

Endometrial Cancer
POLE-mutated
MSI-high
MSS, CN low
CN high
POLE exonuclease domain variation
Ultramutated
Highly responsive to immunotherapy
Excellent prognosis
Hypermutated
Highly responsive to immunotherapy
Variants common in *PTEN, CTNNB1, PIK3CA, KRAS, ARID1A*
TP53 variants common
CCNE1 amplification common
Higher relapse rate
Poor overall survival

Staging of endometrial cancer



FIGO staging




AORTA
PARA AORTIC
LYMPH NODES
COMMON ILIAC ARTERY
1. Duodenum
2. Inferior venacava
3. Aorta
4. Sigmoid mesentry

Who should do the treatment

- Outcomes are best when cancers are screened, diagnosed, staged and managed by Gynae-oncologists
    - No room for trial and error or incomplete surgeries in Oncology
- We now have enough Oncologists to consult and be advised on the treatment to avoid incomplete treatment

Treatment for Endometrial cancer

Stage	Histologic type	Standard treatment	
1	Endometrioid type	Surgery	• TAH and BSO (spare ovaries in young women) • Adjuvant Brachytherapy for High grade types
	Non-Endometrioid type	Surgery	TAH, BSO, Pelvic and Para-aortic lymph nodes, Omentectomy
2		Surgery and Radiation therapy	• TAH, BSO, Pelvic & Para-aortic lymphnode dissection or sampling • Brachytherapy + EBRT
3 & 4		Surgery and radiation therapy	Maximal Surgical Debulking Chemotherapy + Radiotherapy
	High risk non Endometrioid cancers		• Chemotherapy • Radiotherapy

Questions