37th ESMO Congress - Vienna, Austria

September 29, 2012

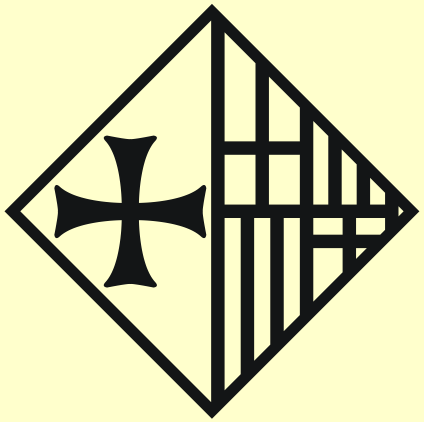
Diagnosis and Management issues in Ovarian Cancer

New Insights into Ovarian Cancer Pathology

Jaime Prat, M.D., Ph.D., F.R.C.Path.

Hospital de la Santa Creu i Sant Pau

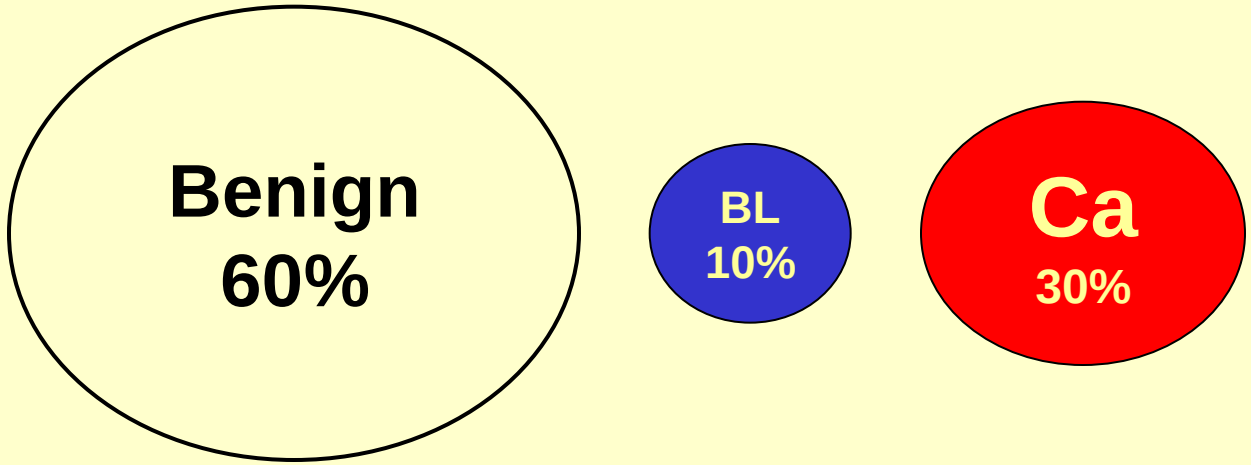
Autonomous University of Barcelona, Spain



Ovarian Epithelial Tumors

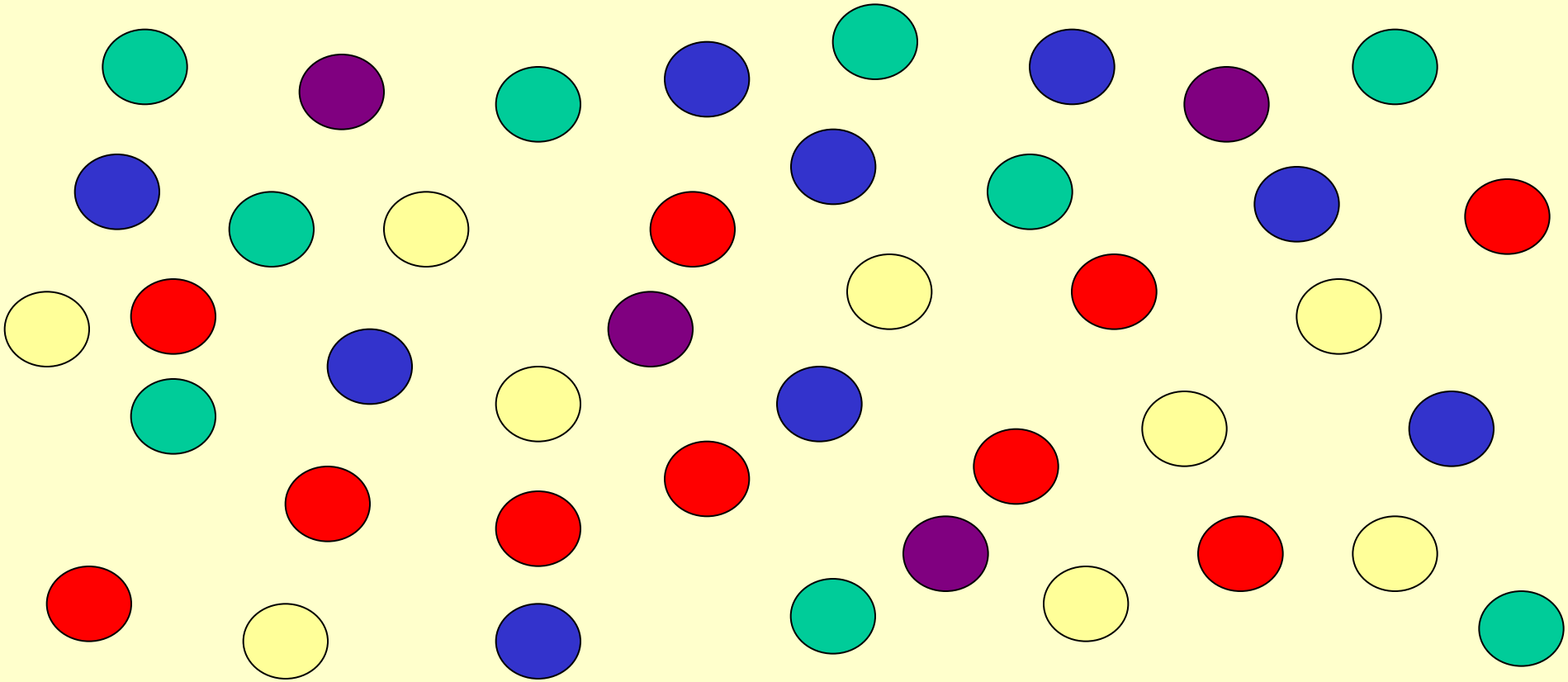
WHO 1999 and 2003

Serous
Mucinous
Endometrioid
Clear cell
Transitional
Squamous
Mixed
Undifferentiated



EPITHELIAL OVARIAN TUMORS
A heterogeneous group

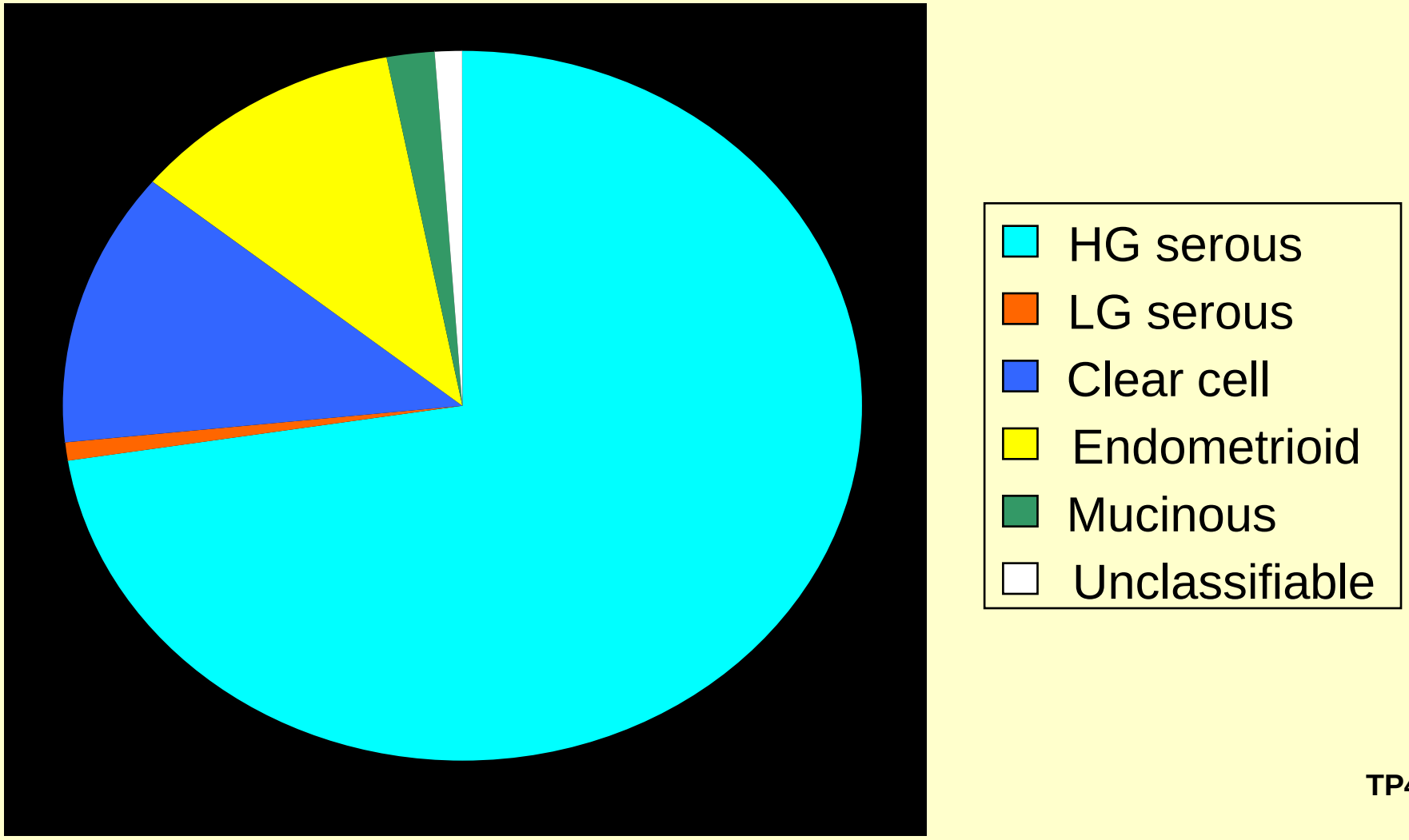
Histologic type, Precursor lesions, Genetic alterations …



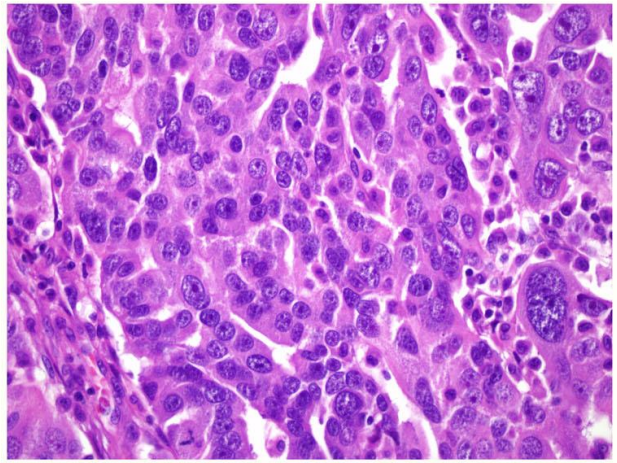
Histologic Subtypes of Ovarian Carcinomas

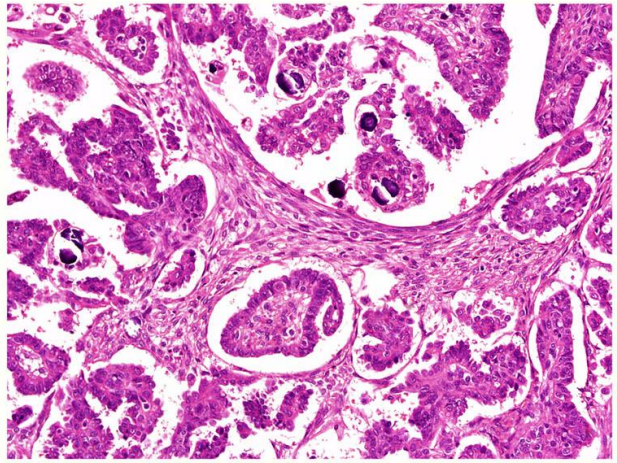
- Serous – high grade
- Serous – low grade
- Clear cell
- Endometrioid
- Mucinous

New classification: Frequency



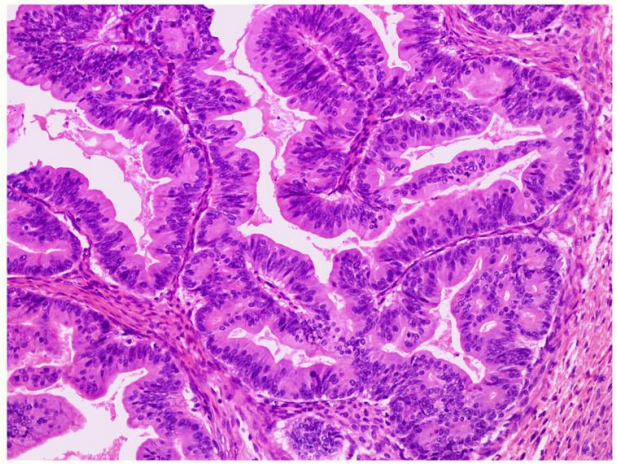
HGC

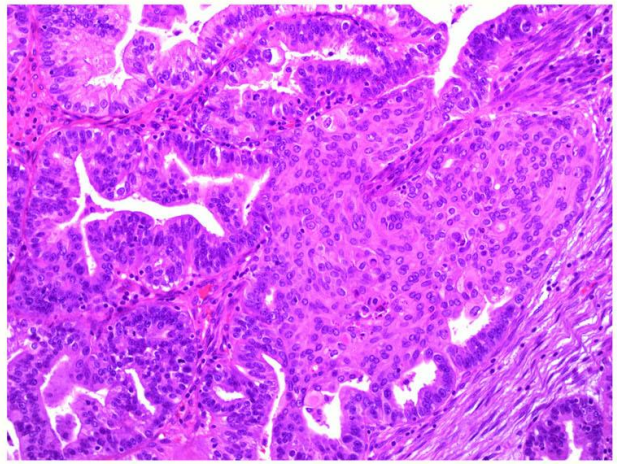




LGSC

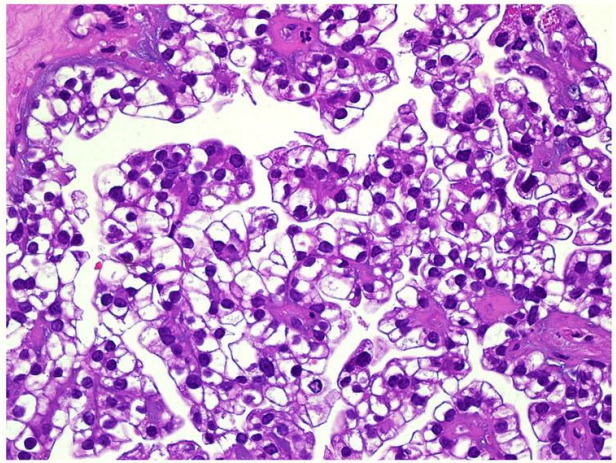
MC





EC

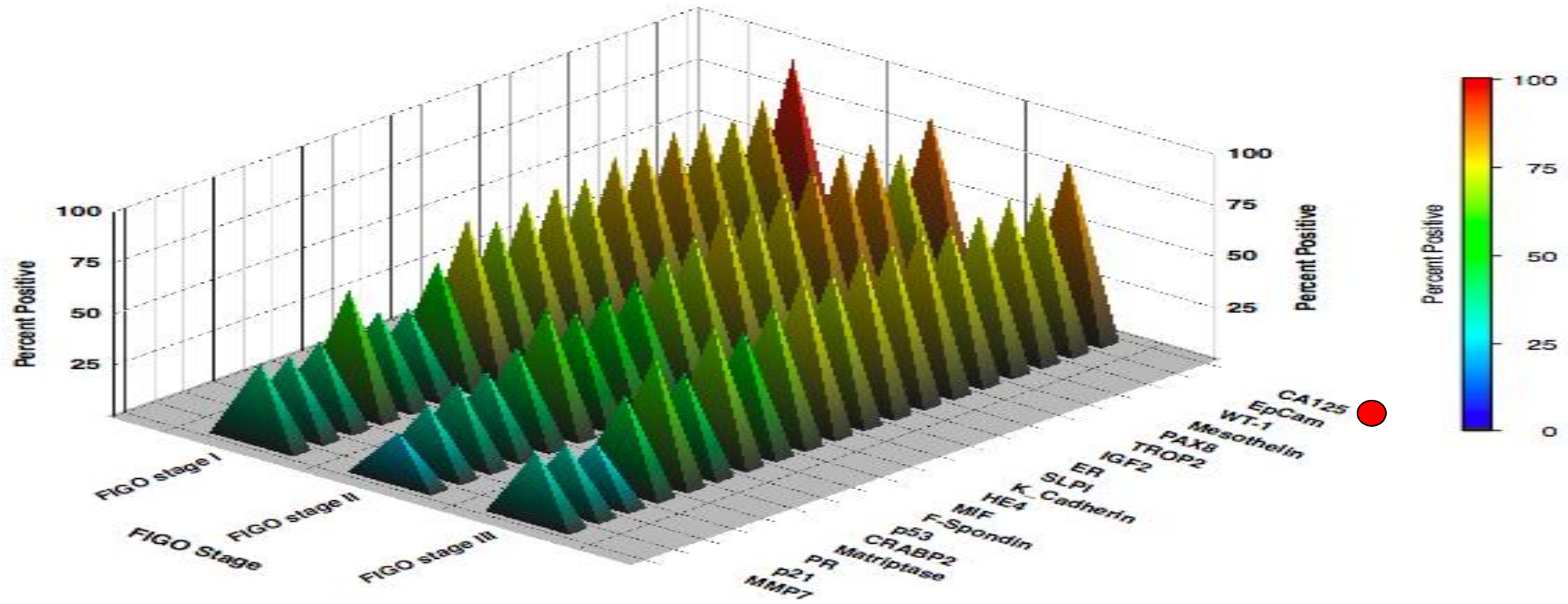
CCC



These subtypes differ from each other with respect to:

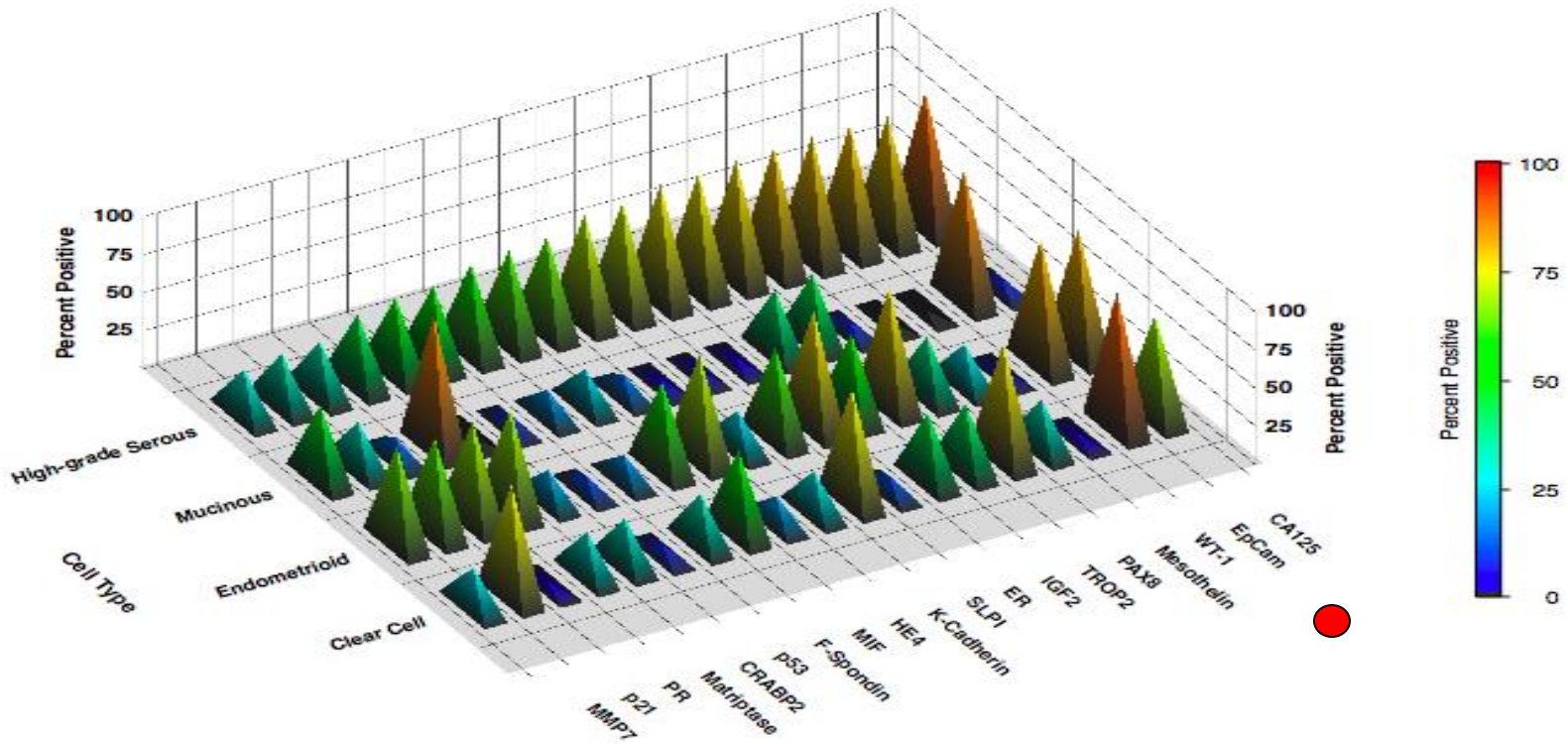
1. Risk factors and precursor lesions
2. Patterns of spread
3. Molecular genetic alterations
4. Response to chemotherapy
5. Outcome

High-grade Serous Cancers



Köbel M et al.
PLoS Med 2008; 5:e232

Biomarker profiles across subtypes



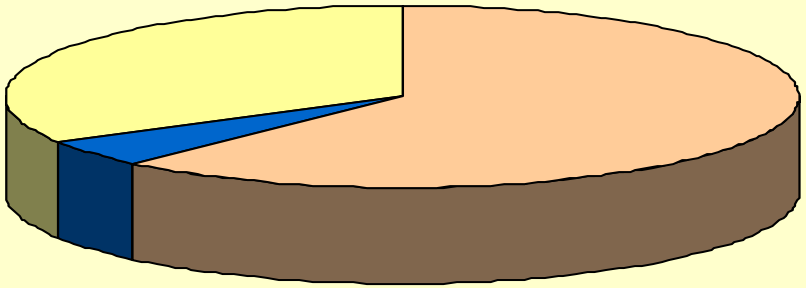
Köbel M et al.
PLoS Med 2008; 5:e232

Serous Carcinoma

HEREDITARY SUSCEPTIBILITY TO OVARIAN CANCER

BRCA2 (30%)

Lifetime risk 15-30%

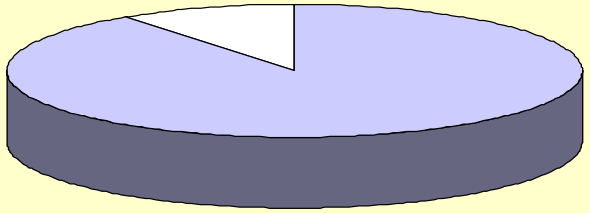


BRCA1 (65%)

Lifetime risk 30-60%

HNPCC (7%)

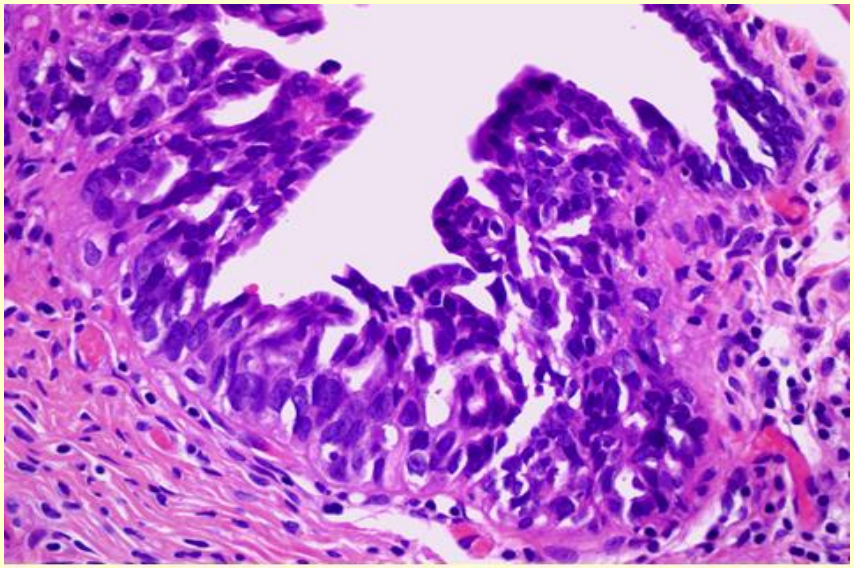
Hereditary (10%)

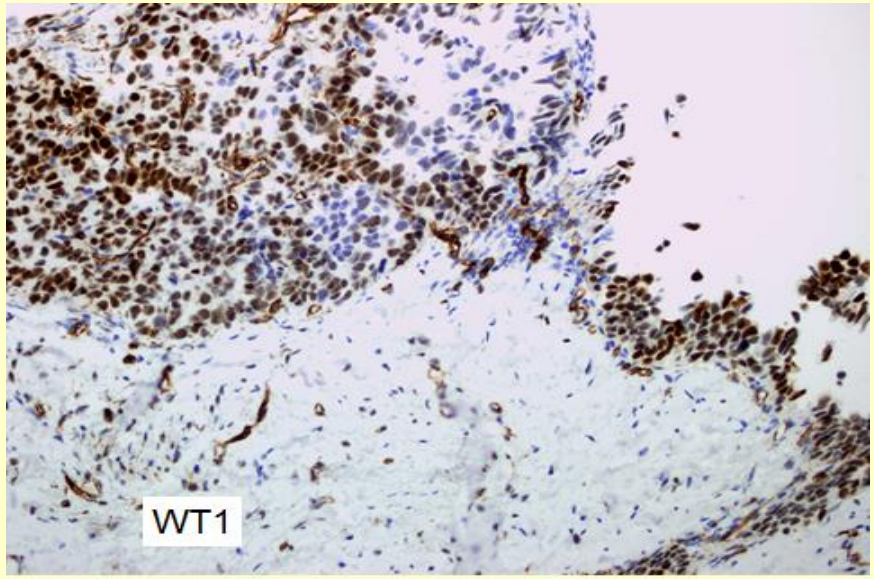


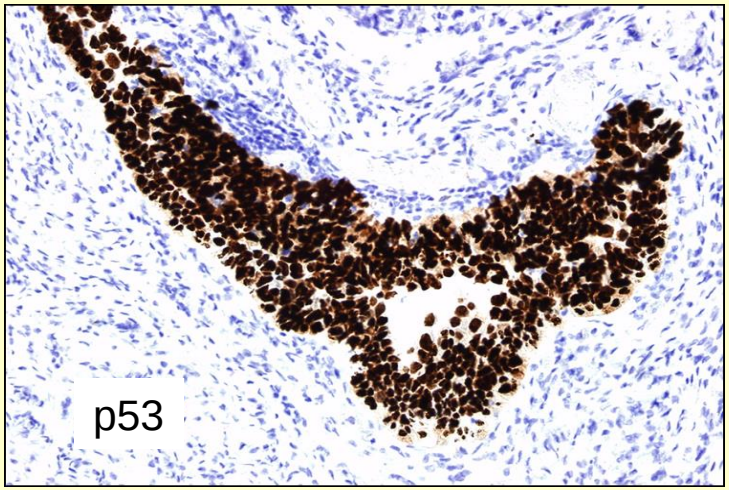
Sporadic (90%)

Rebbeck TR, Lynch HT, et al. NEJM 2002

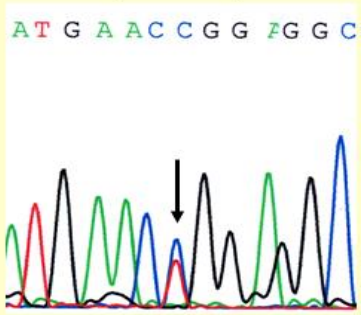
Serous “Intraepithelial” Carcinoma STIC

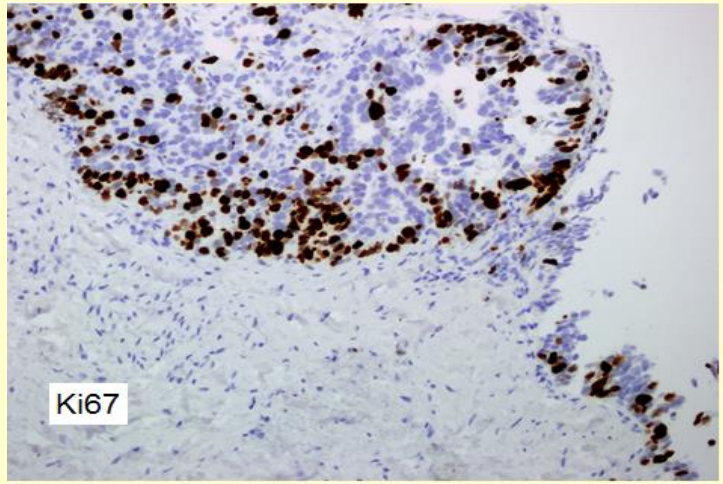




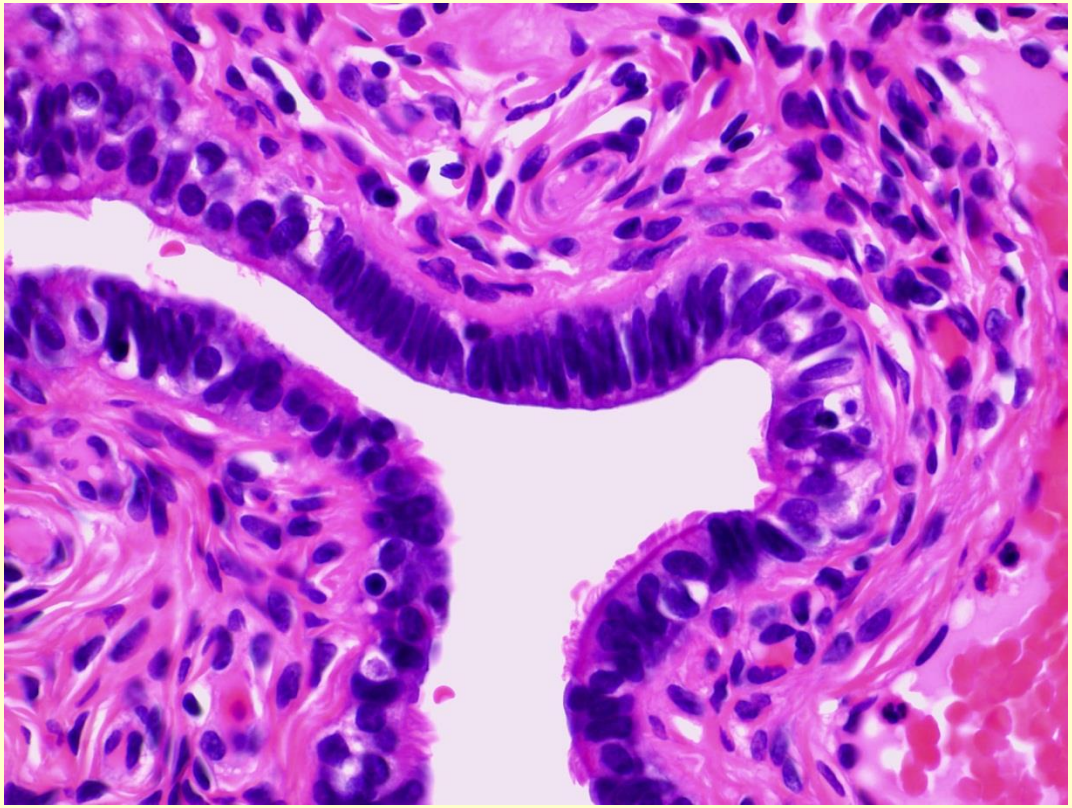


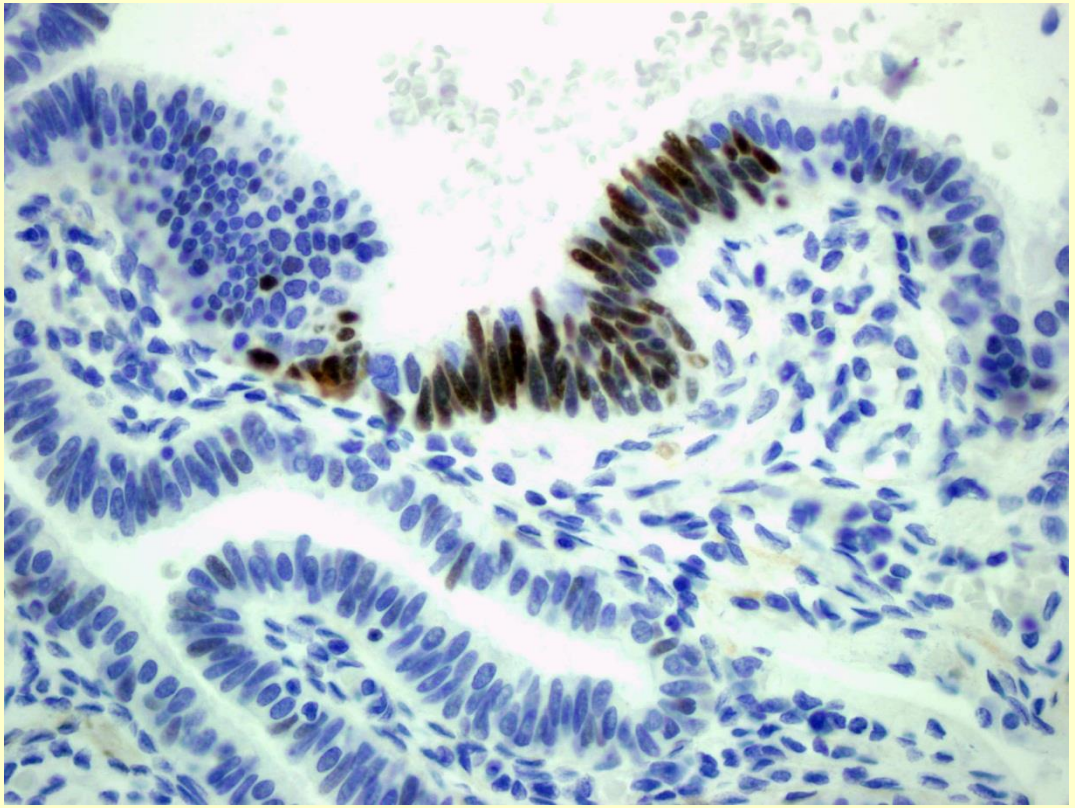
P53
R248W
(Exon 7)





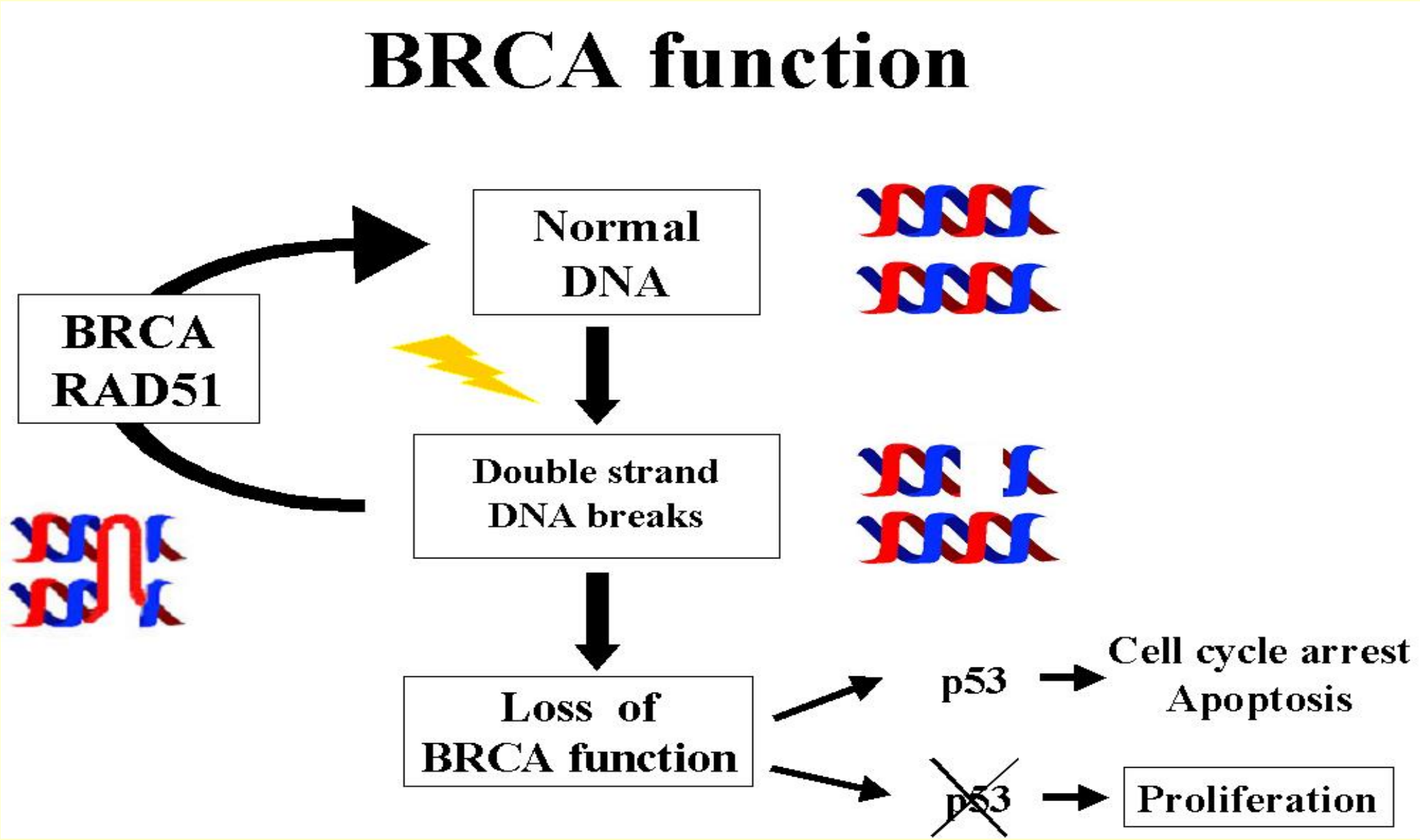
How about less than STIC?





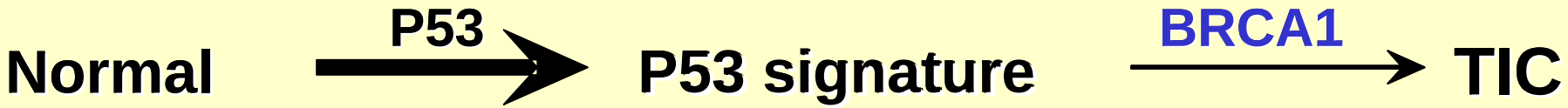
P53 Signature

BRCA function



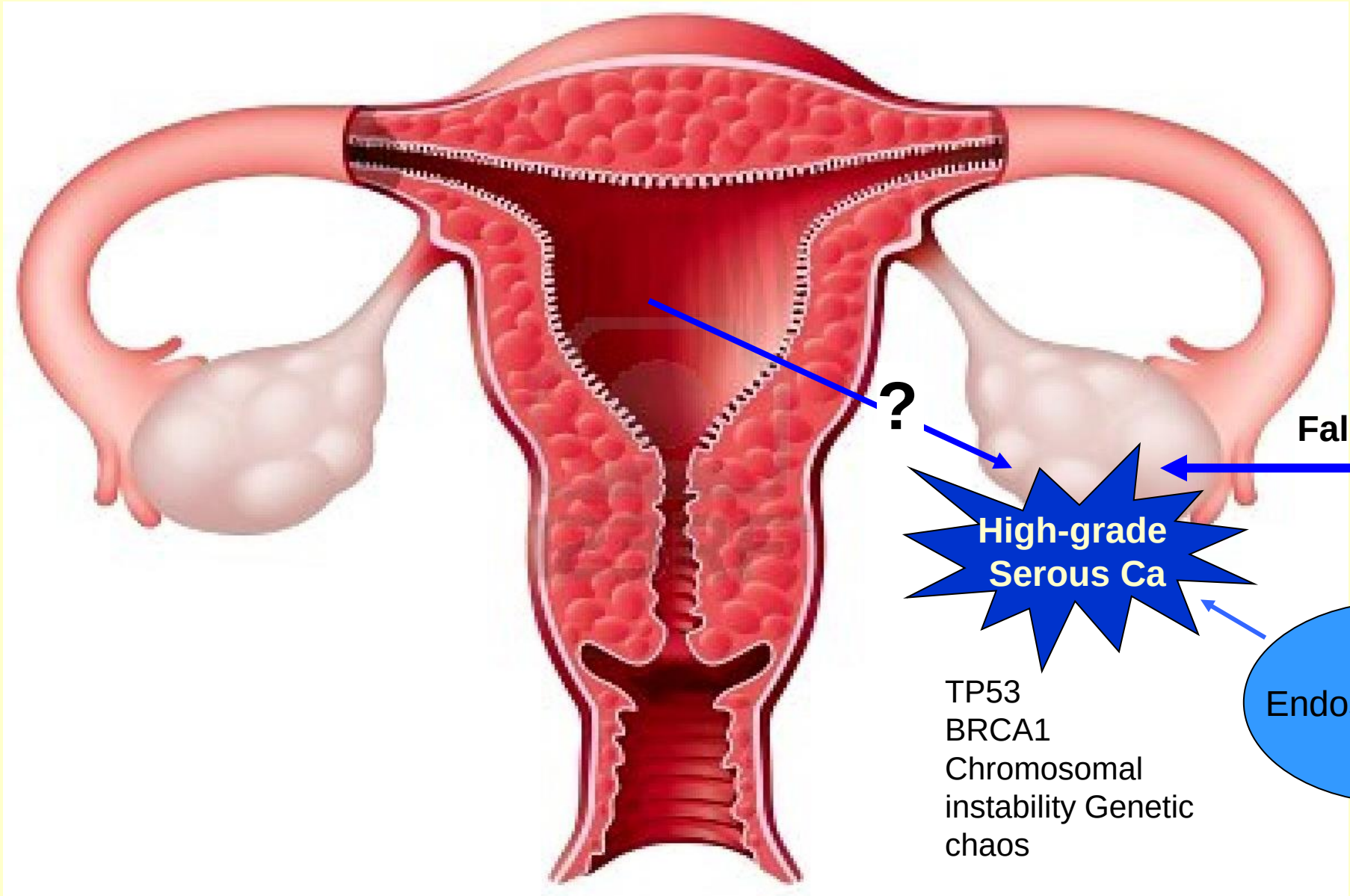
BRCA Promotes P53 Signature to TIC

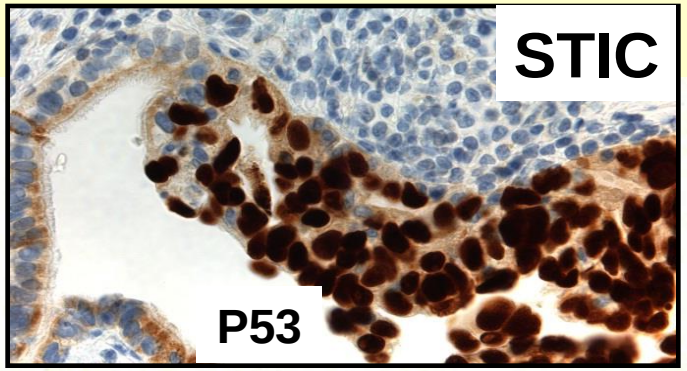
Hereditary ： BRCA1 mutation constitutive

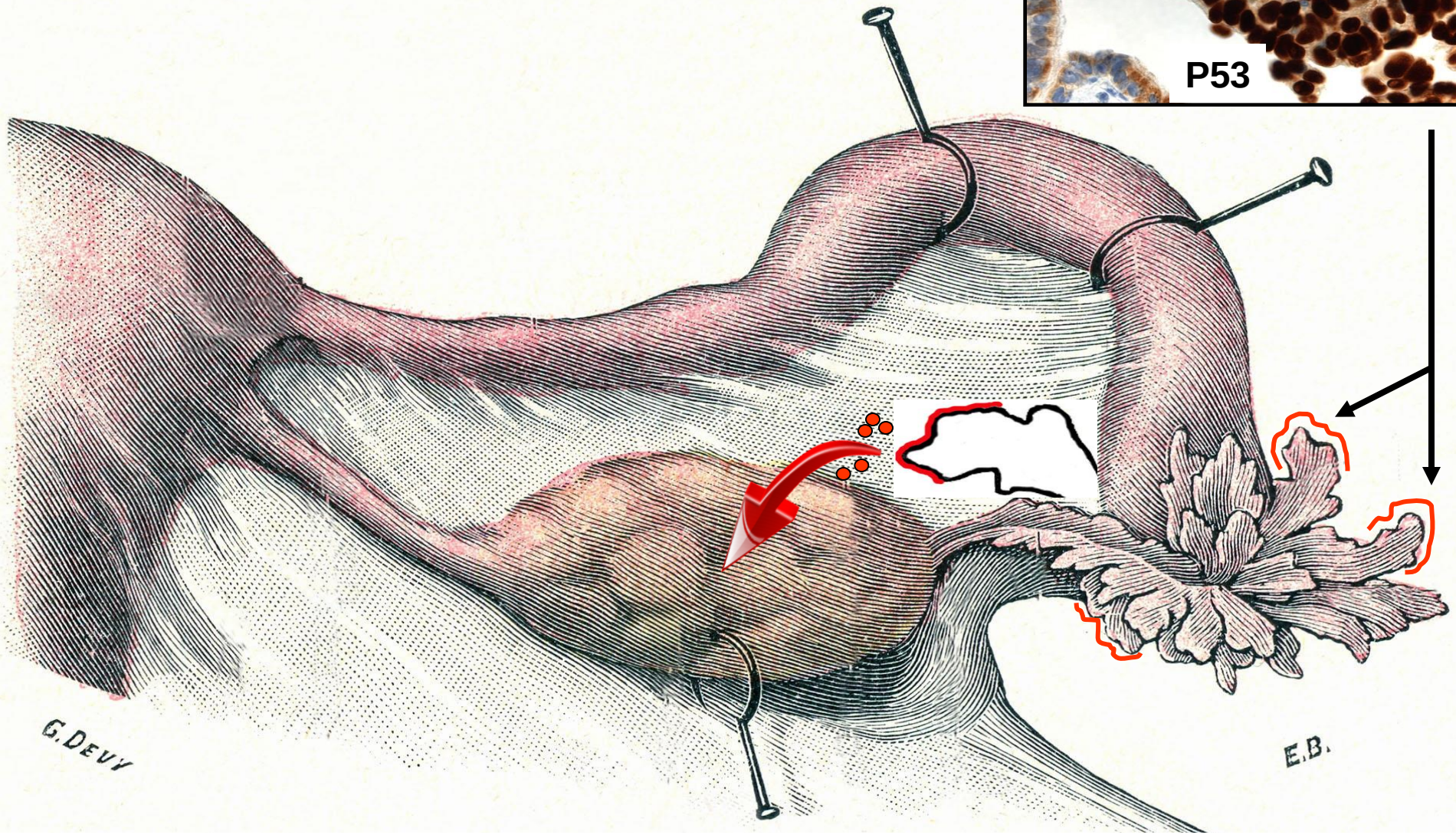


Sporadic ： BRCA1 methylation/mutation new event

Classification of Gyn Cancers based on Origin and Mutations

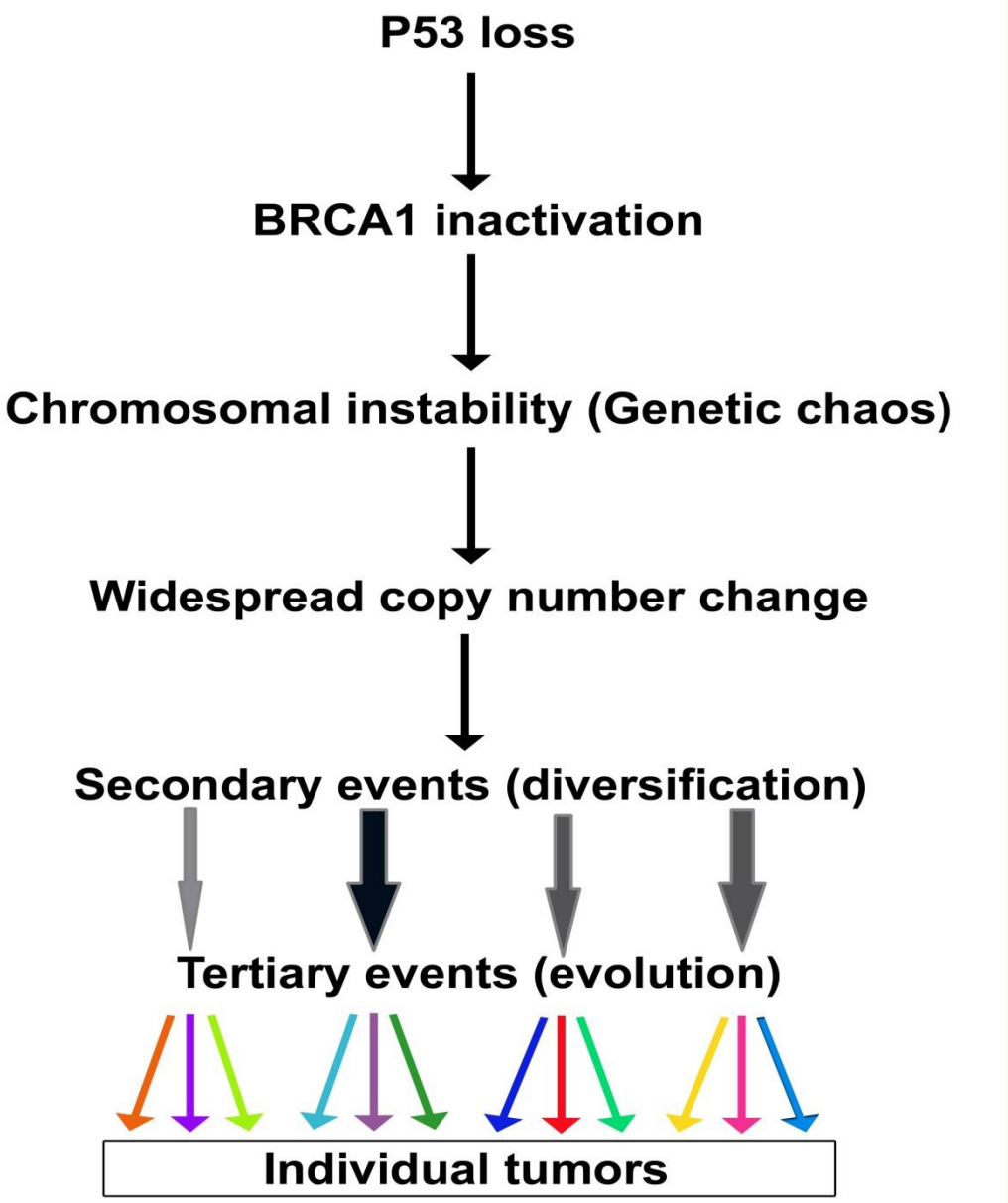






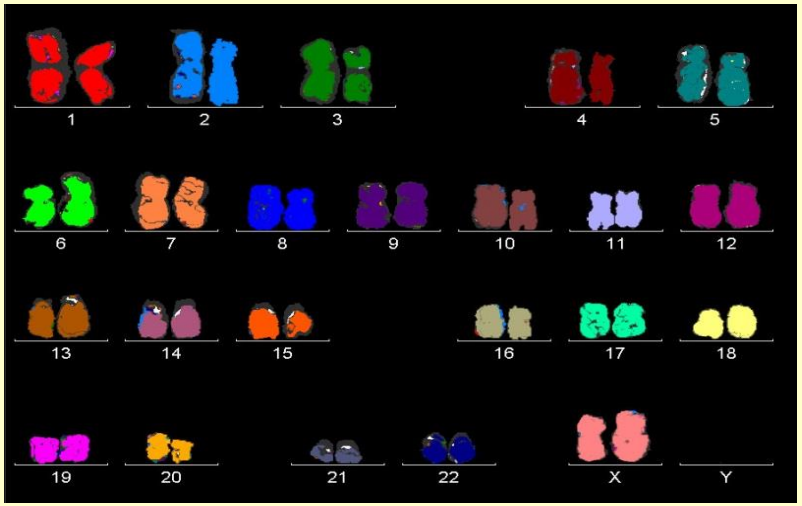
High Grade Serous Carcinoma

HGSC – Pathogenetic Model

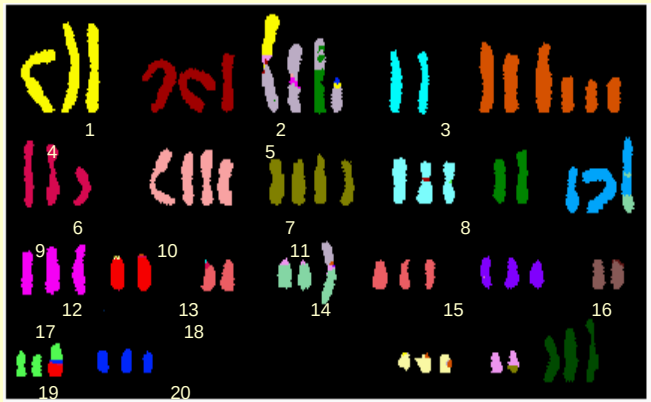


DDL Bowtell Nature Rev Cancer 2010

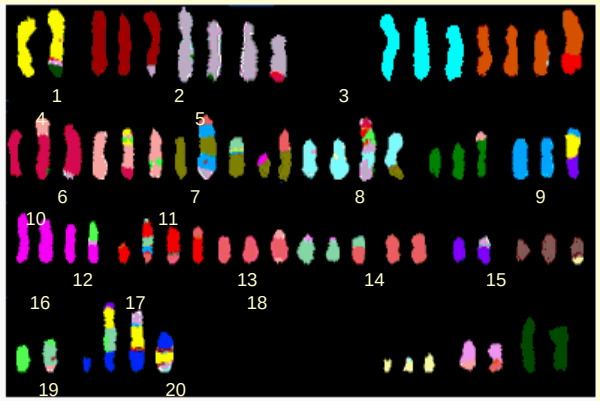
Chromosomes from six ovarian cancers showing: chromosomal instability



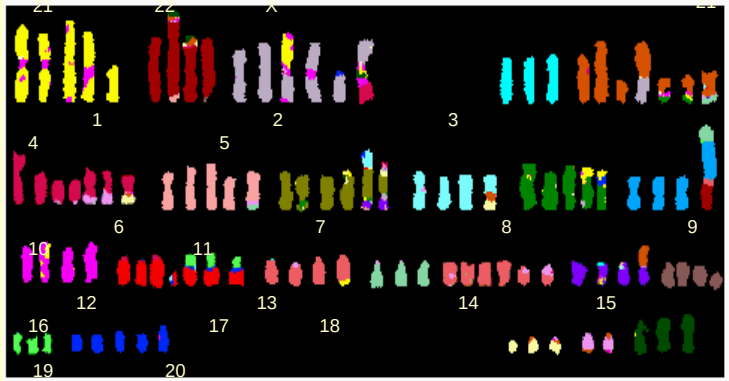
A



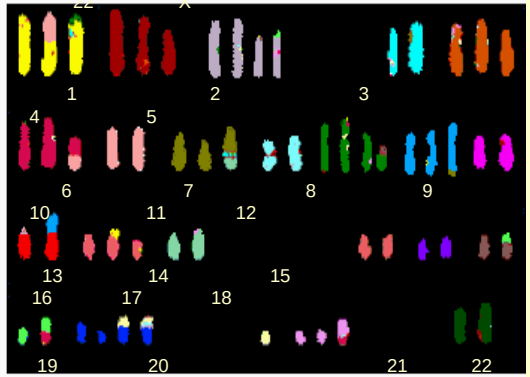
B



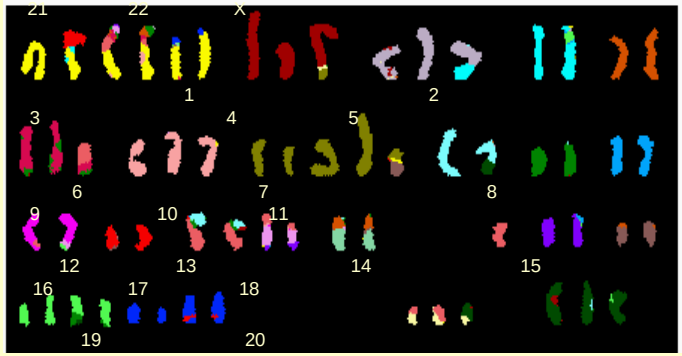
C



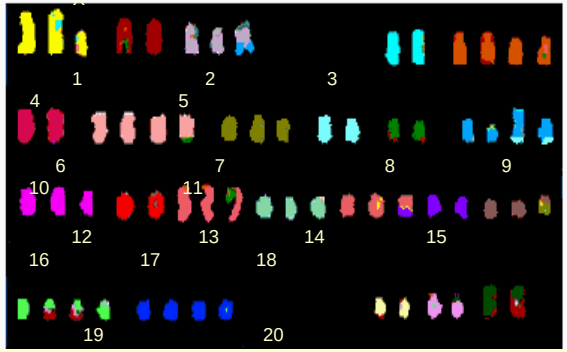
D

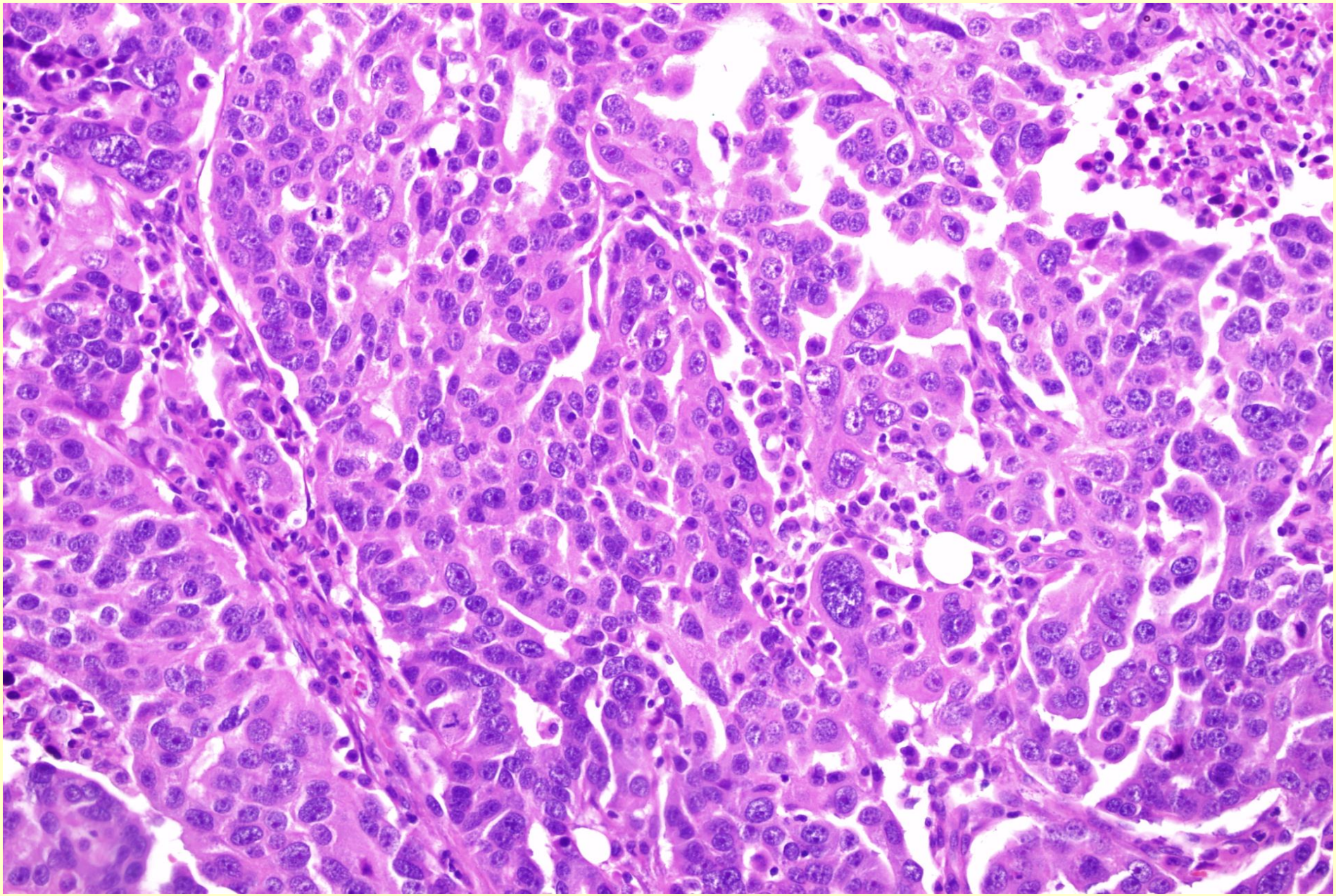


E

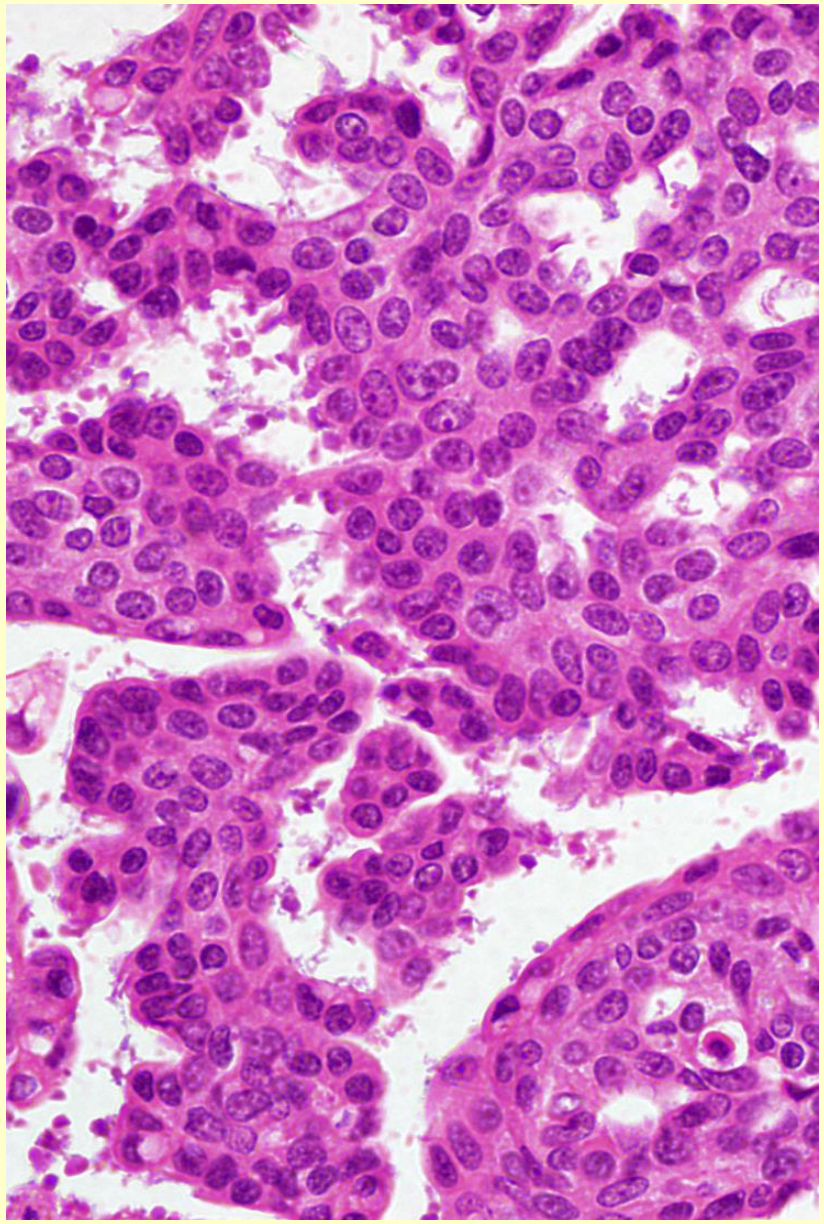


F

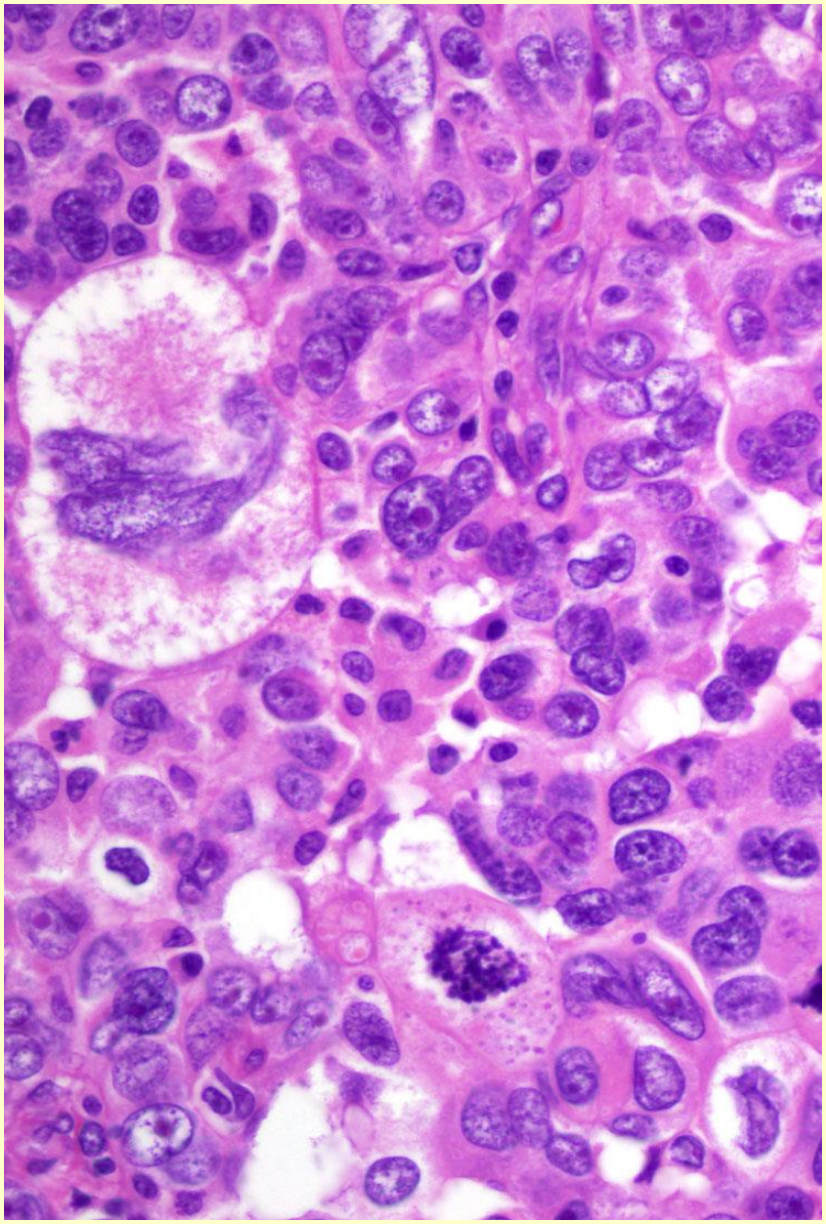




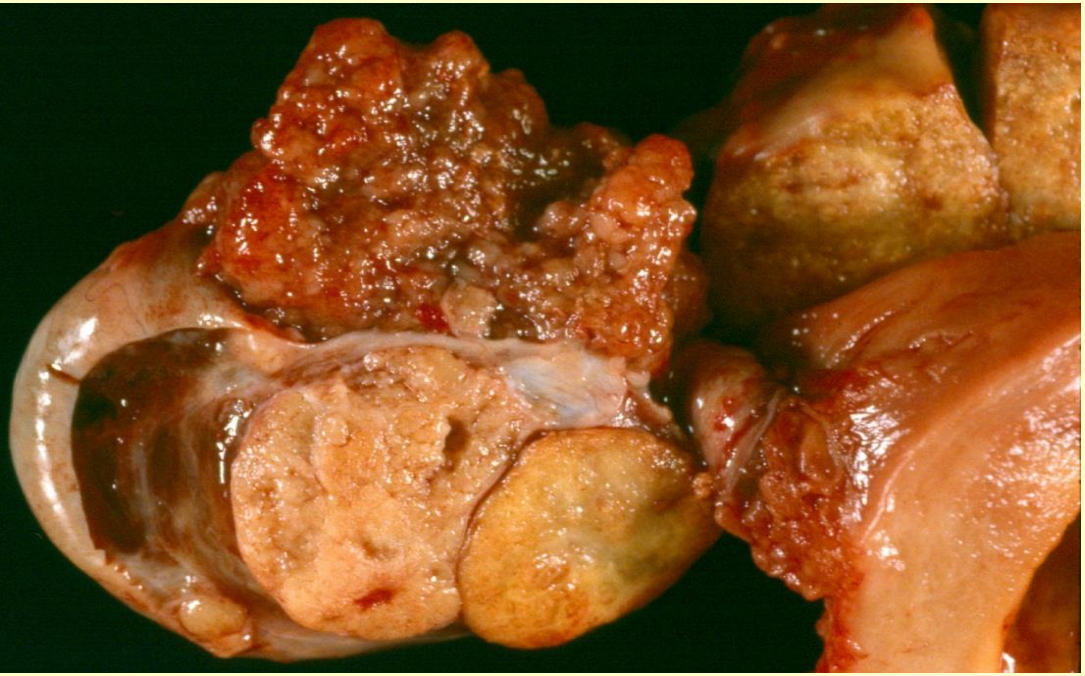
Serous carcinoma, G3



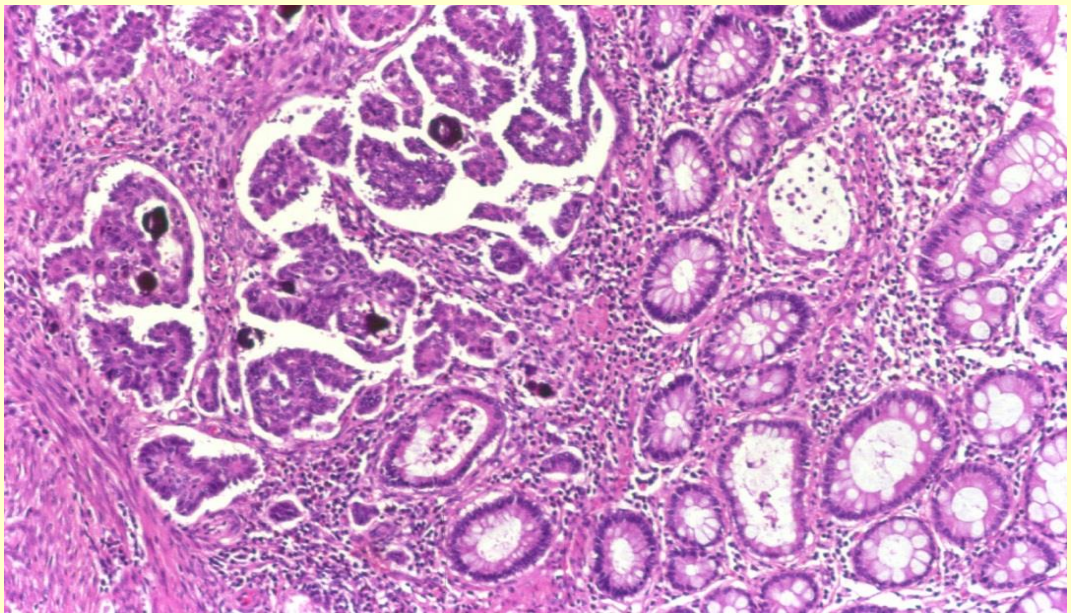
Low grade

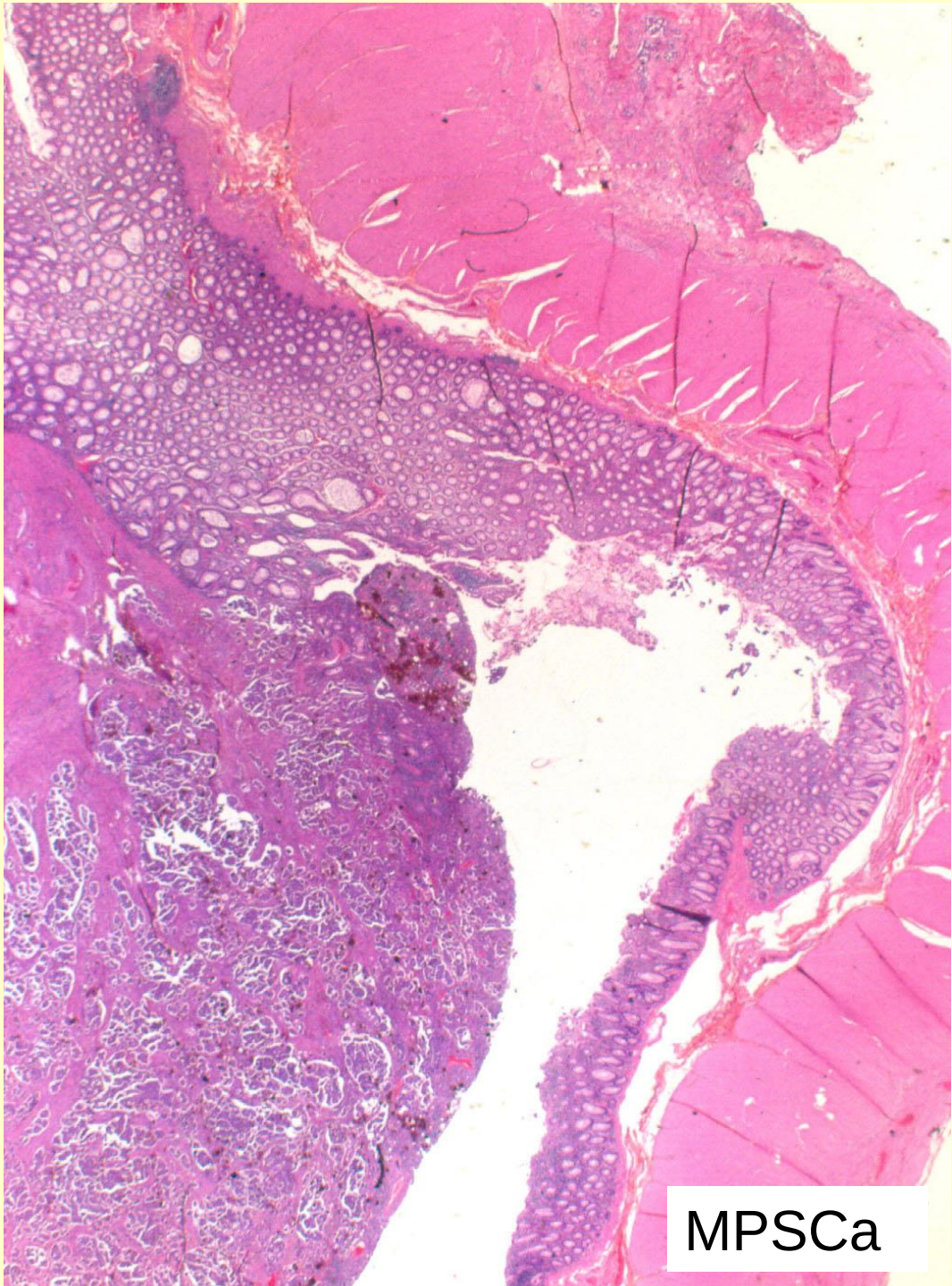


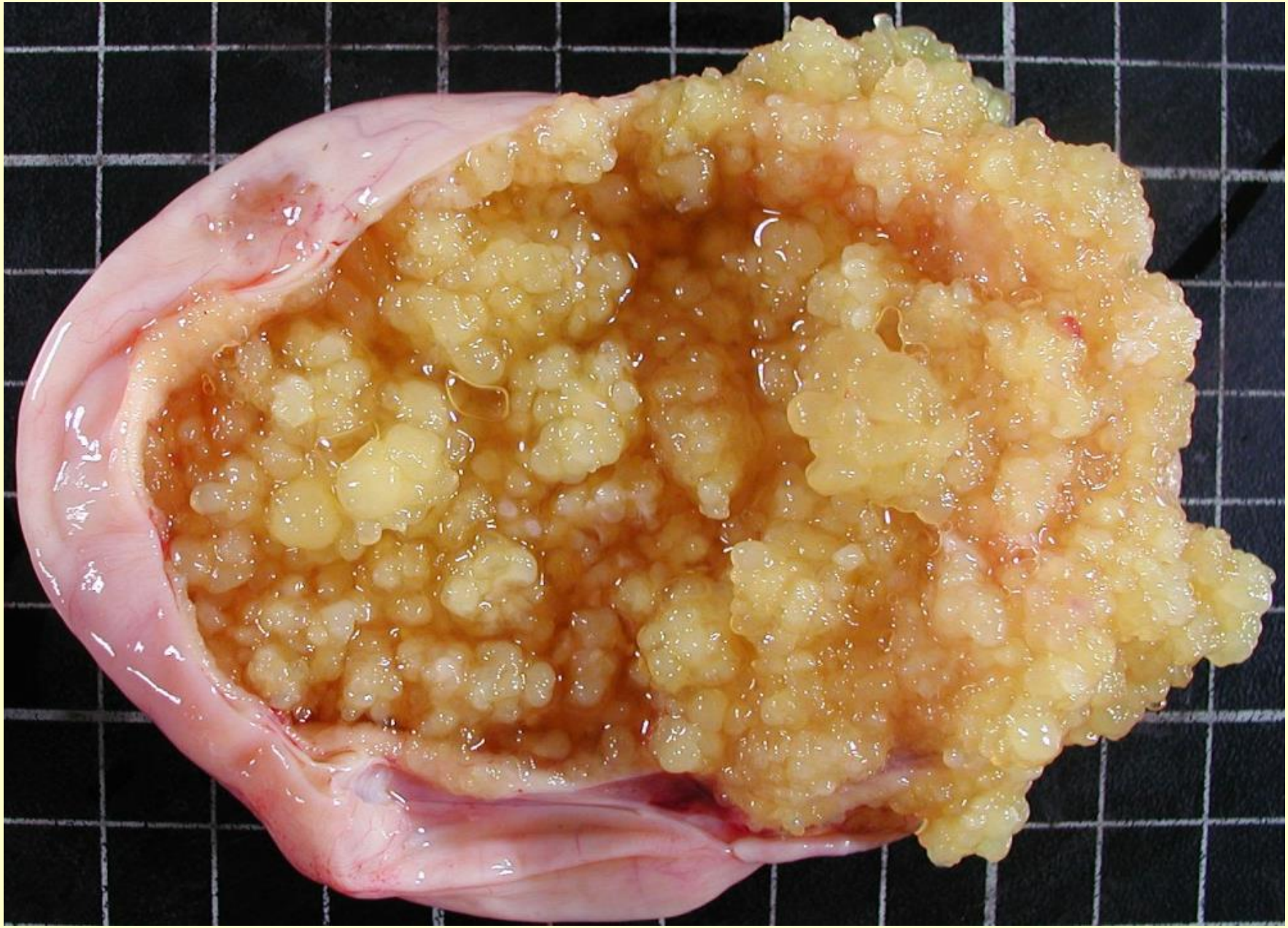
High grade



SBT + MPSCa





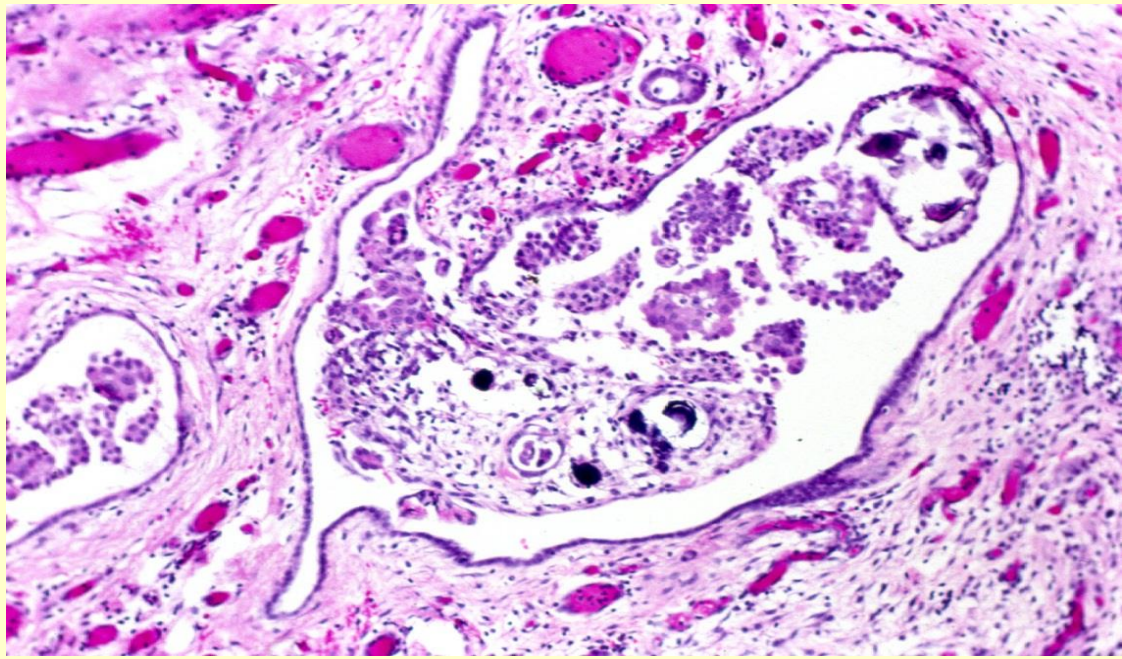


Serous Borderline Tumor

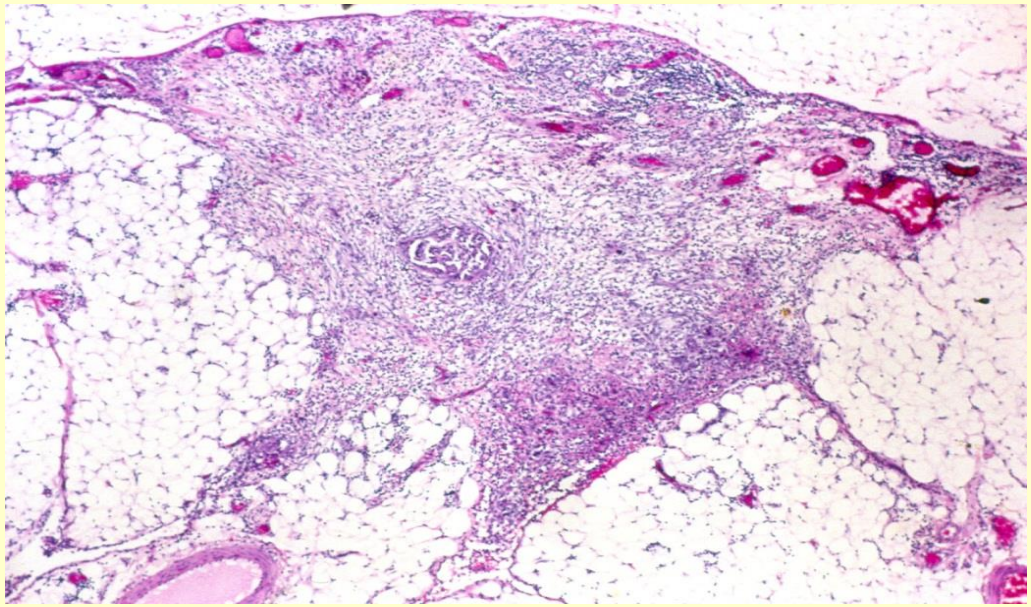
Peritoneal Implants (SBT)

- Non-invasive
  - Epithelial
  - Desmoplastic
- Invasive

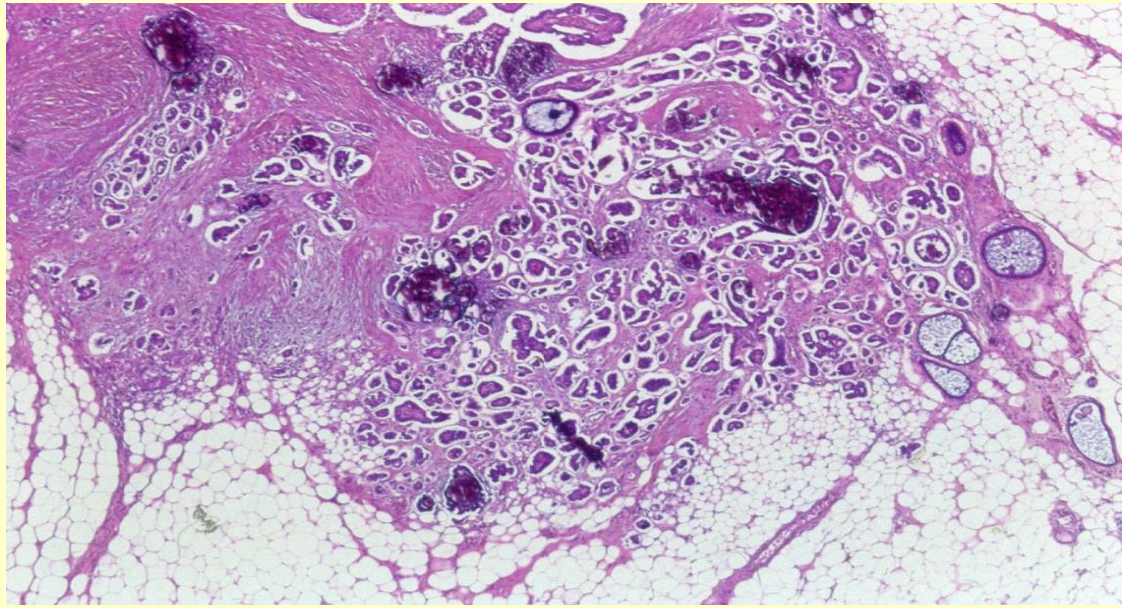
Bell DA, et al
Cancer 1988; 62:2212



Noninvasive epithelial implant



Noninvasive (desmoplastic) implant



Invasive implant

Serous Tumors

(Pathogenesis - Dualistic model)

Bg → SBT → SBT-MP → MP Ca (Inv) Low Gr Serous Ca

KRAS and *BRAF* mutations (70%)

High Grade Serous Ca

p53 mutations, LOH 17q (80%)

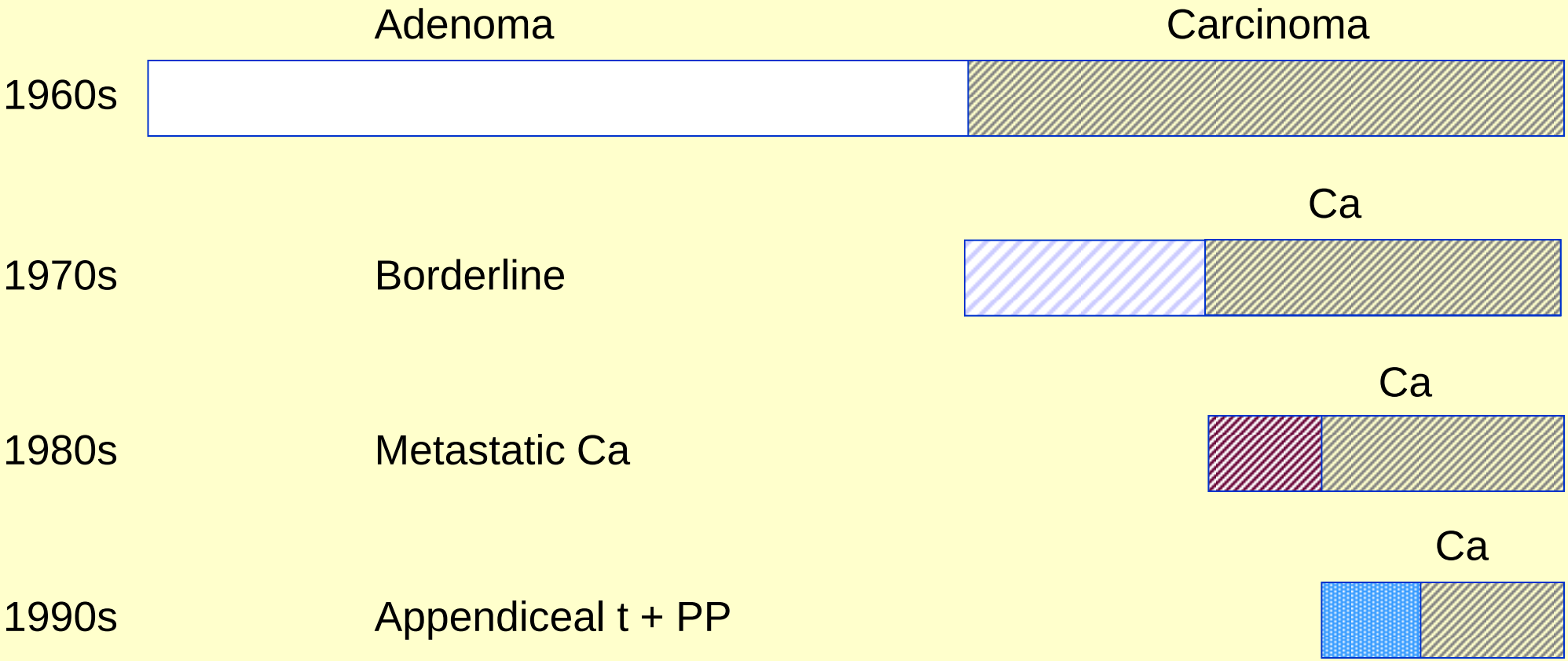
BRCA inactivation (80%)

HER-2/neu amplification/overexpression

Singer et al
Am J Pathol 2002

Mucinous Tumors of the Ovary

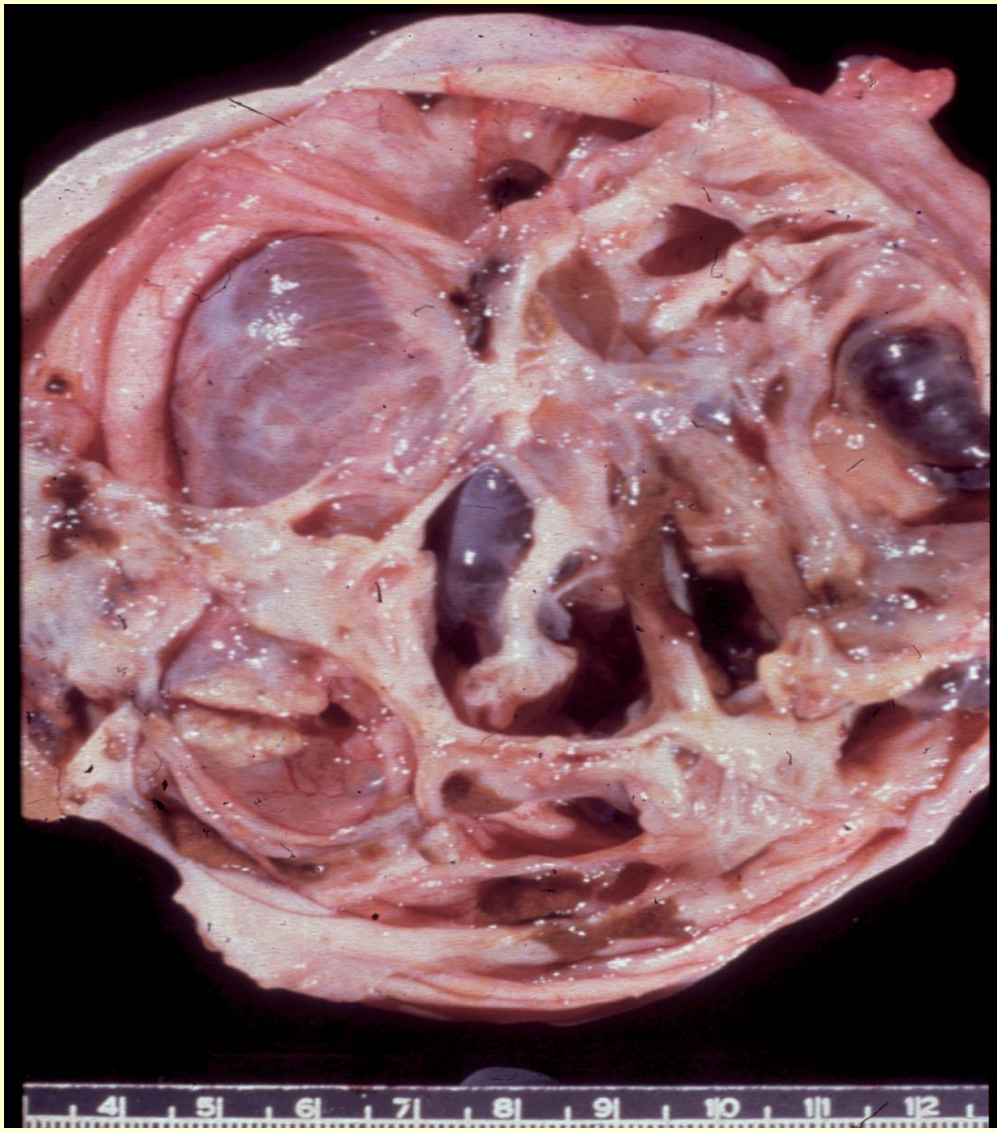
(From benign to malignant)

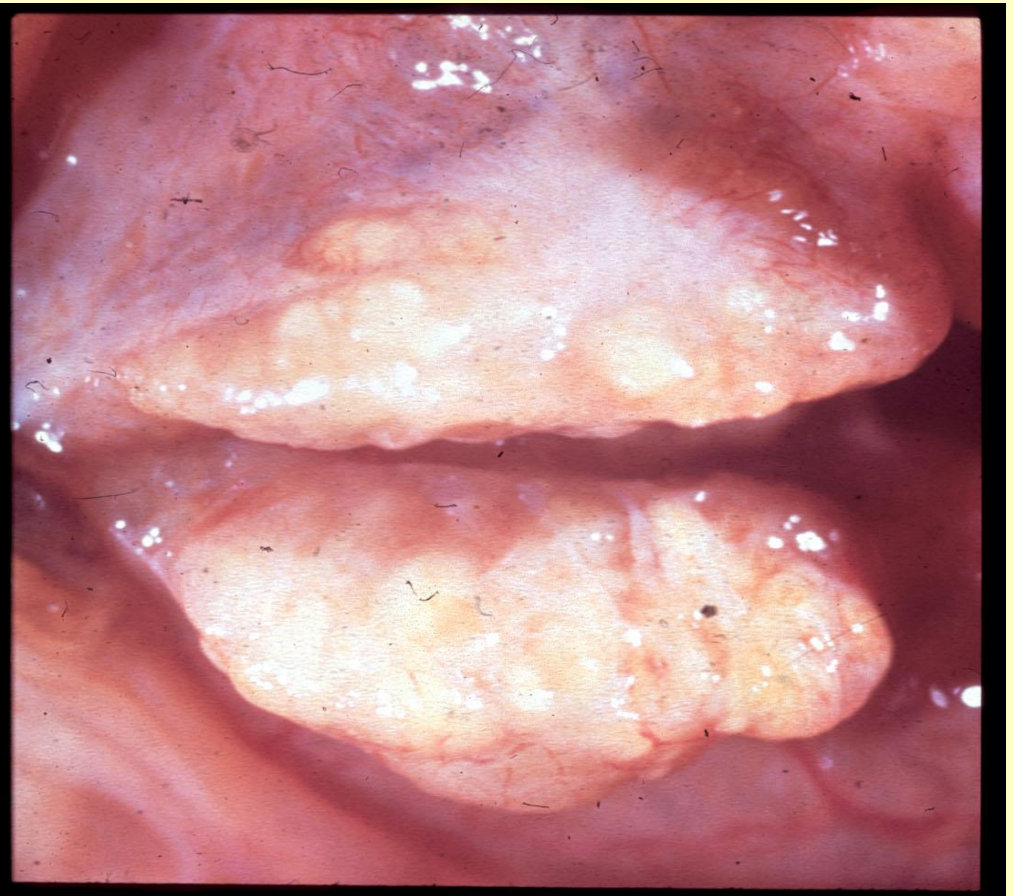


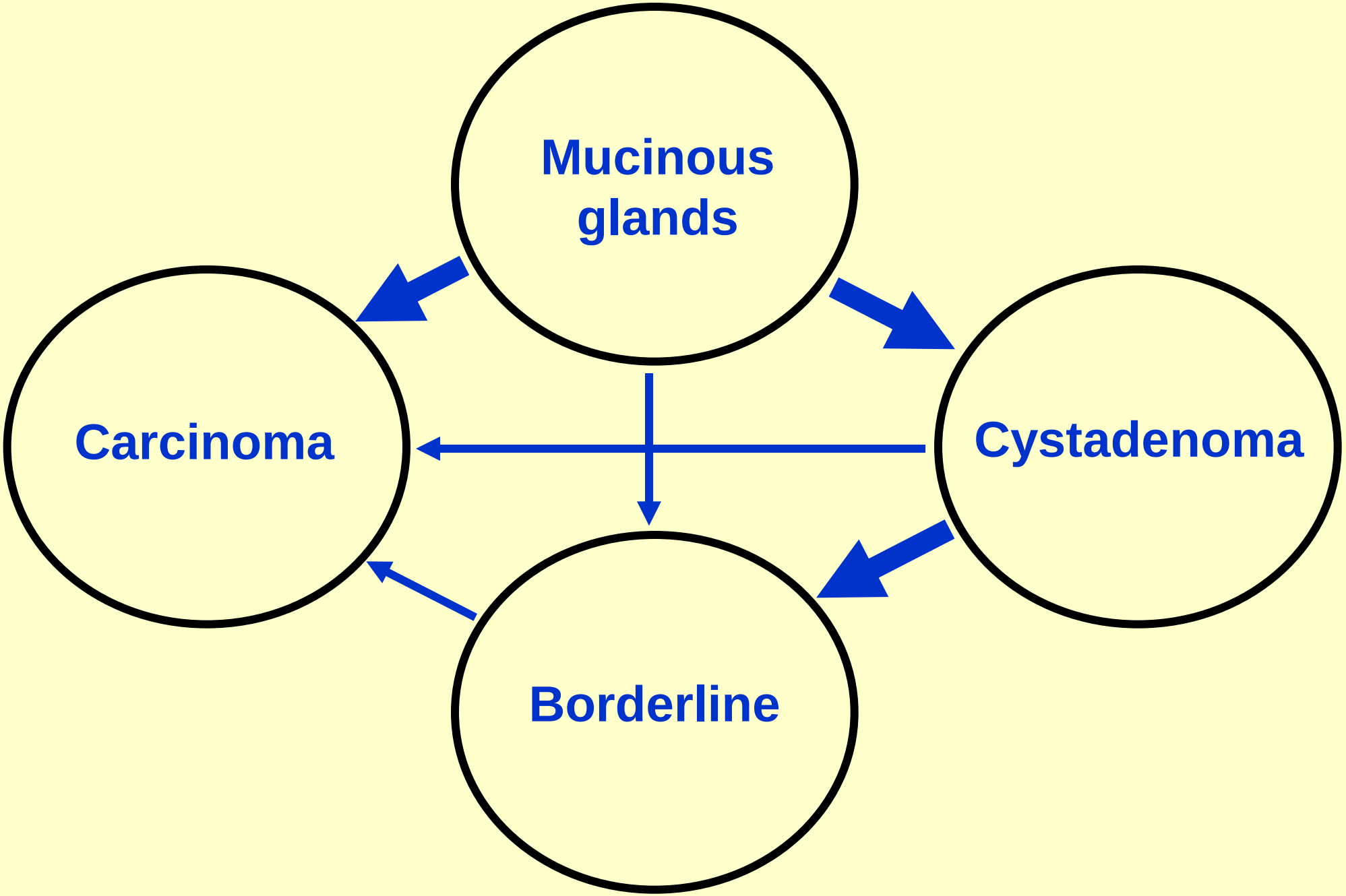
Mucinous Tumors
(Ovary)

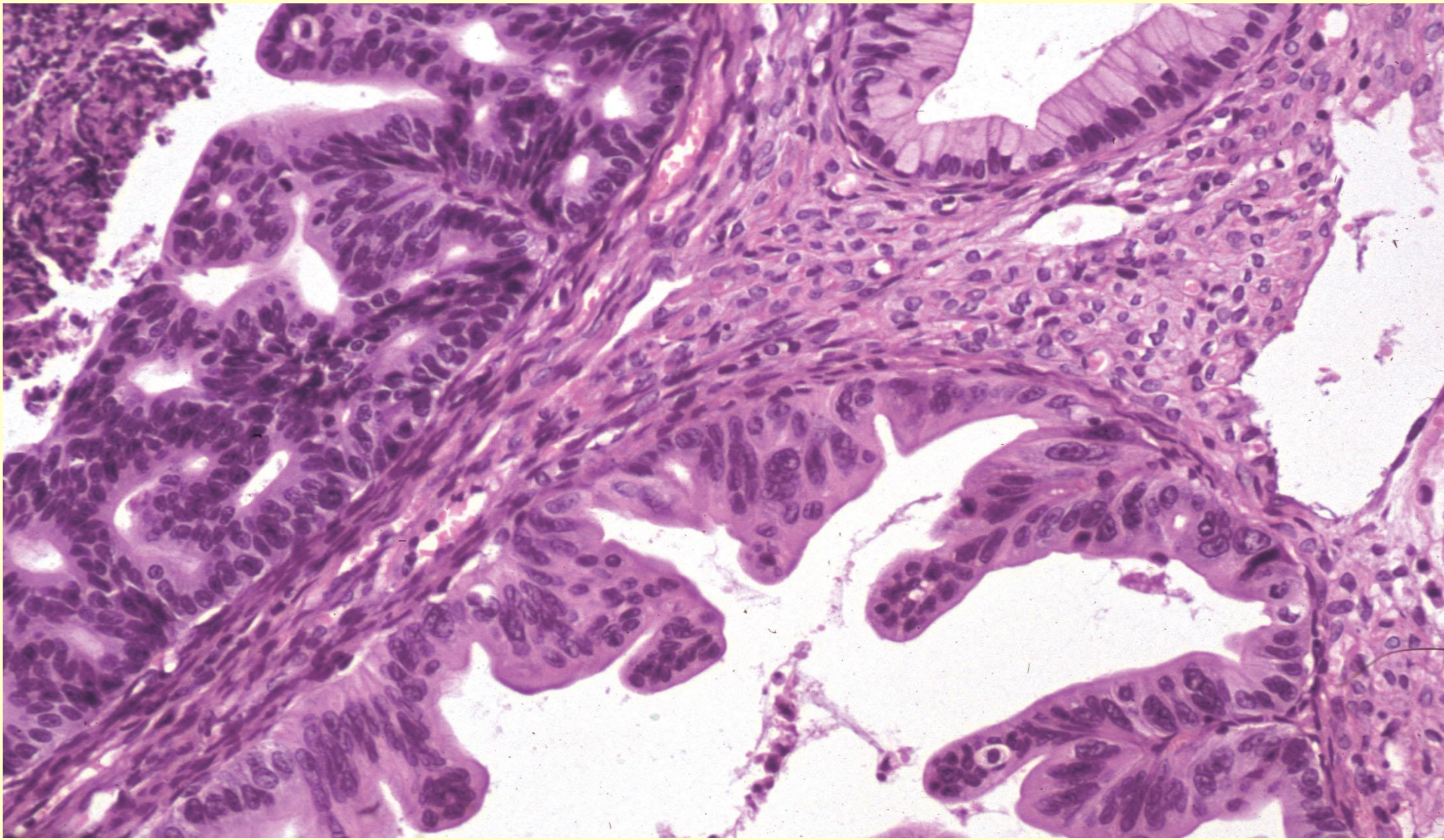
• Benign	75%	80%
• Borderline	10%	17%
• Carcinomas	15%	3%

Koonings, 1998


4
5
6
7
8
9
10
11
12

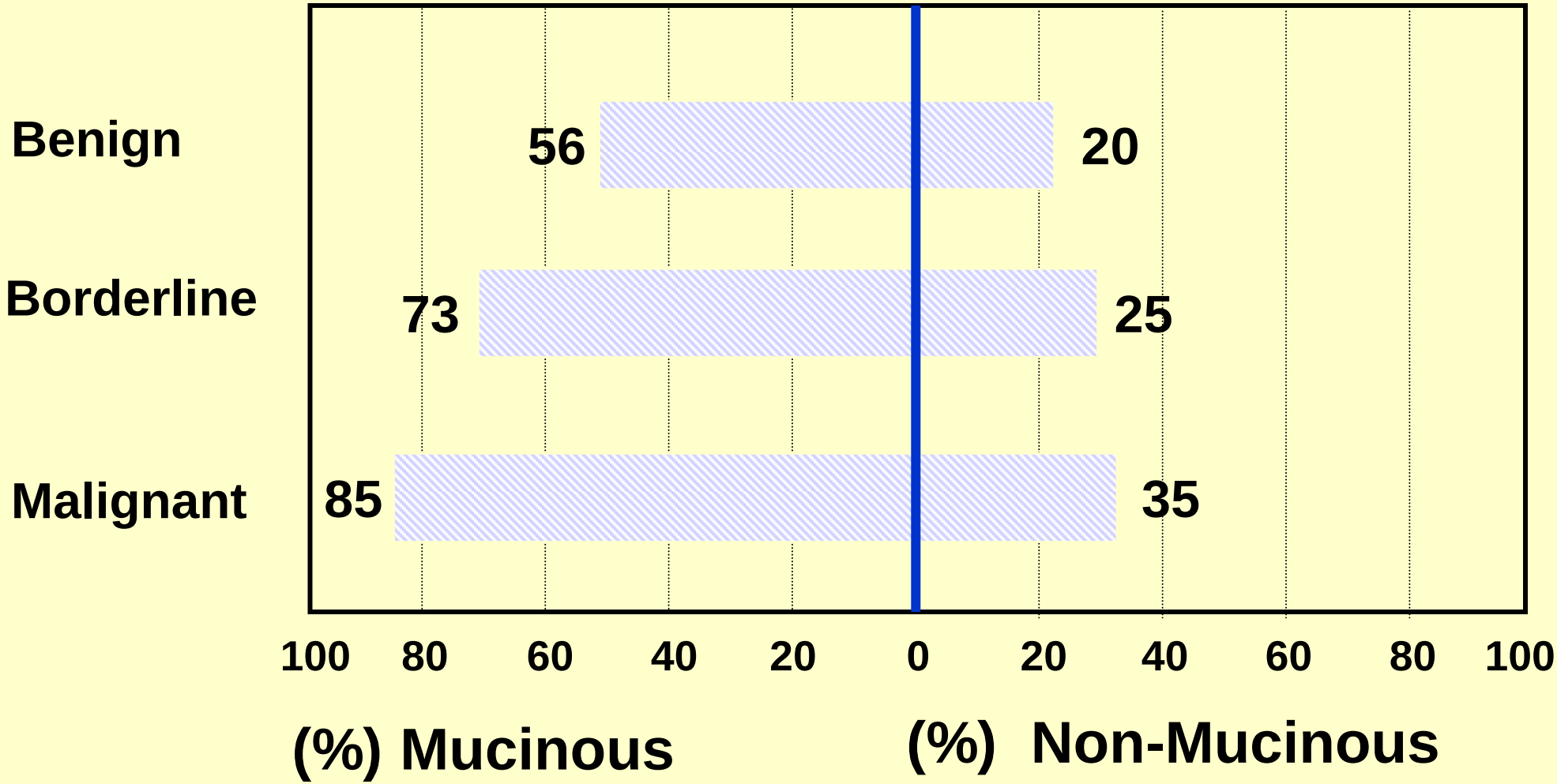



Mucinous glands
Carcinoma
Cystadenoma
Borderline



Epithelial Ovarian Tumors

K-ras Mutations (12, 13)



Cuatrecasas M, et al. Cancer 1997

These subtypes differ from each other with respect to:

1. Risk factors and precursor lesions
2. Patterns of spread
3. Molecular genetic alterations
4. Response to chemotherapy
5. Outcome

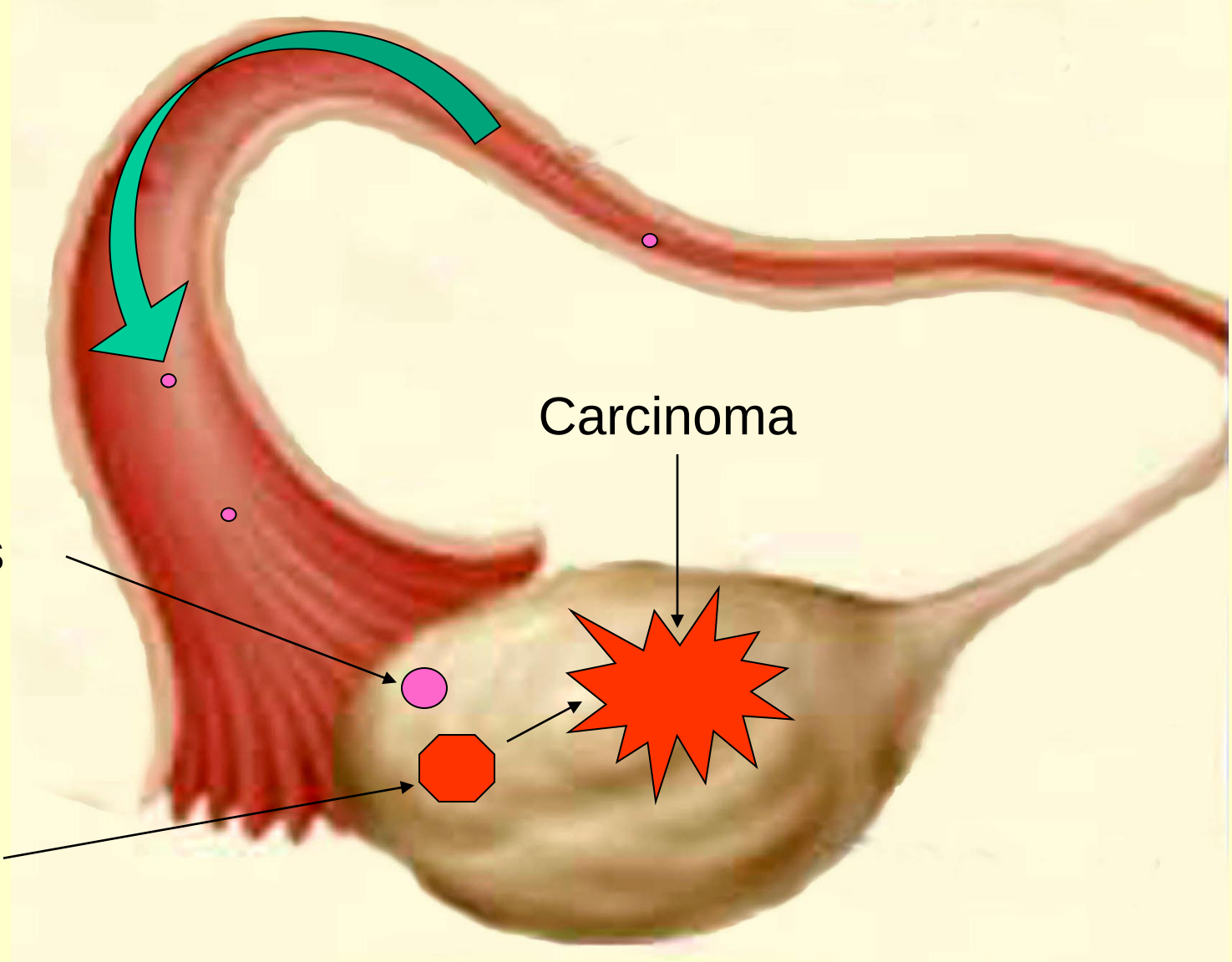
Ovarian Carcinomas:

Stage at presentation (early vs advanced) according to Histologic Subtype

Stage	Clear Cell	Endometrioid	Mucinous	Low-Grade Serous	High-Grade Serous	Carcinoma NOS
I-II	26.2%	29.4%	8.5%	1.9%	30%	4.0%
III-IV	4.9%	3.5%	1.1%	4.9%	84.2%	1.4%
All	10.4%	10.3%	3.6%	3.5%	70%	2.1%

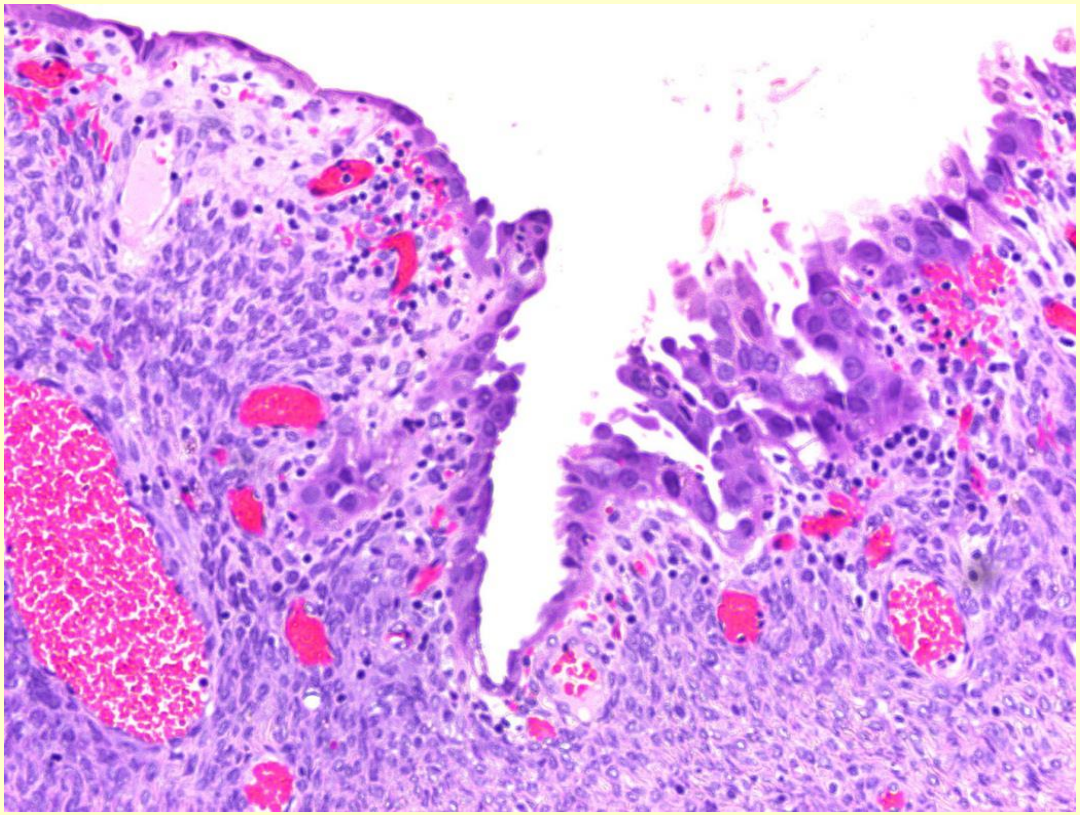
Gilks CB et al.
Mod Pathol 2009; 22:215A

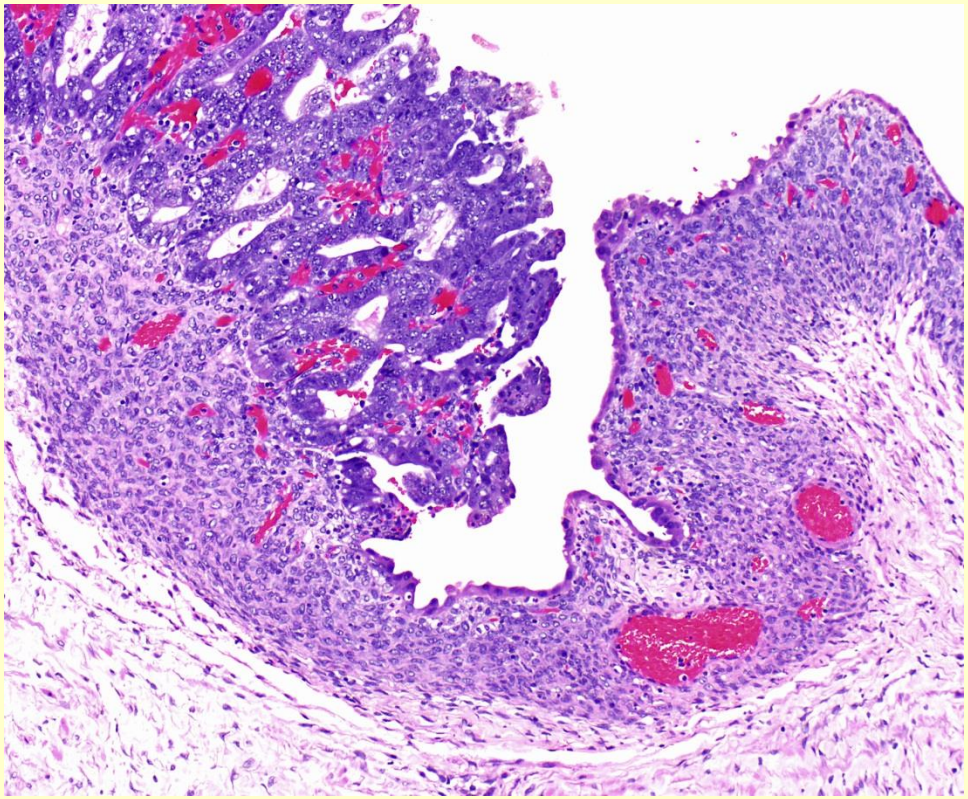
Endometrioid and Clear Cell Tumors develop from Ovarian Endometriosis



Ovarian Atypical Endometriosis → Endometrioid or Clear Cell Carcinomas

15-32% of cases

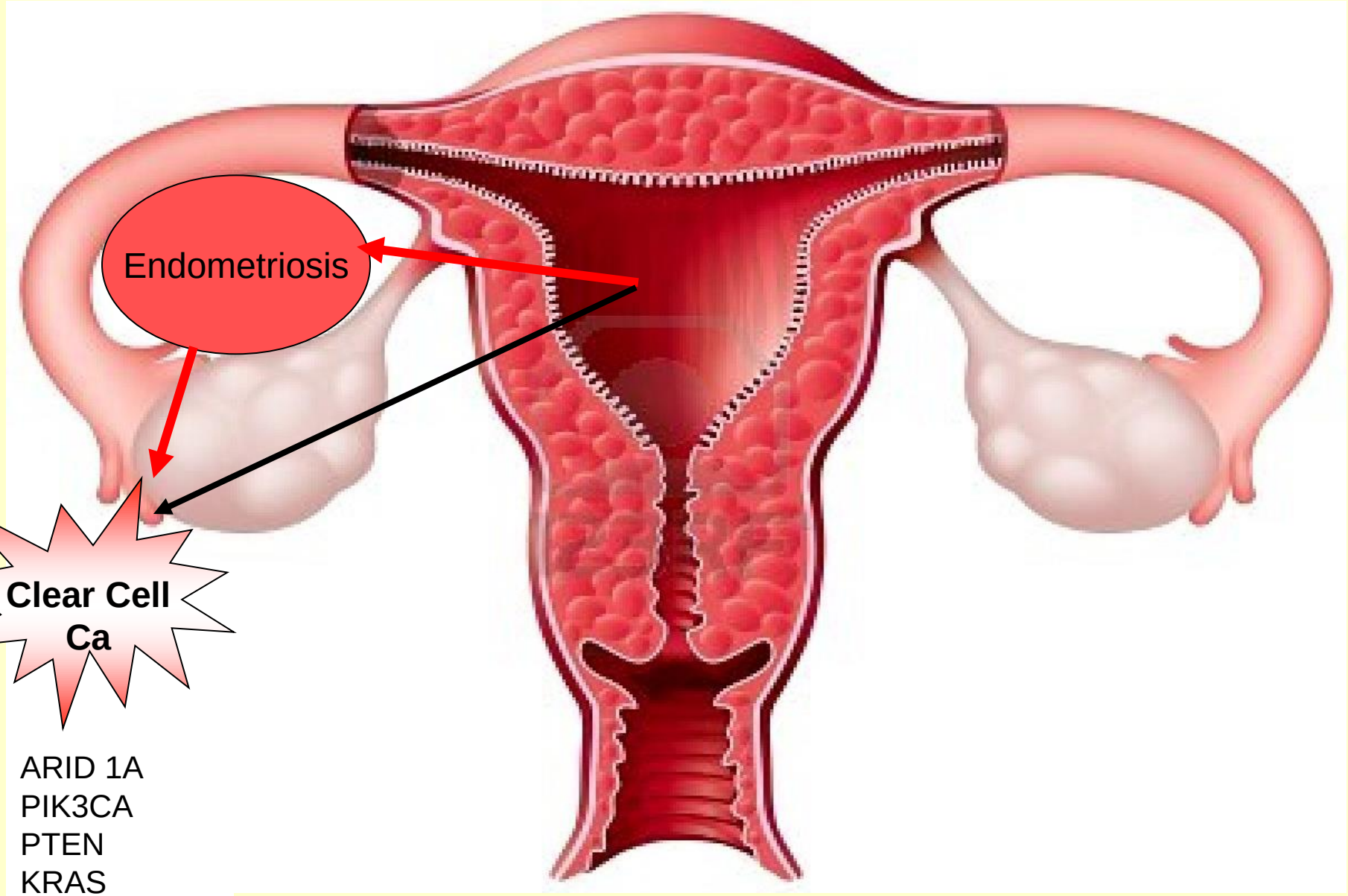




Genetic Alterations of Endometrioid Carcinomas of the Ovary

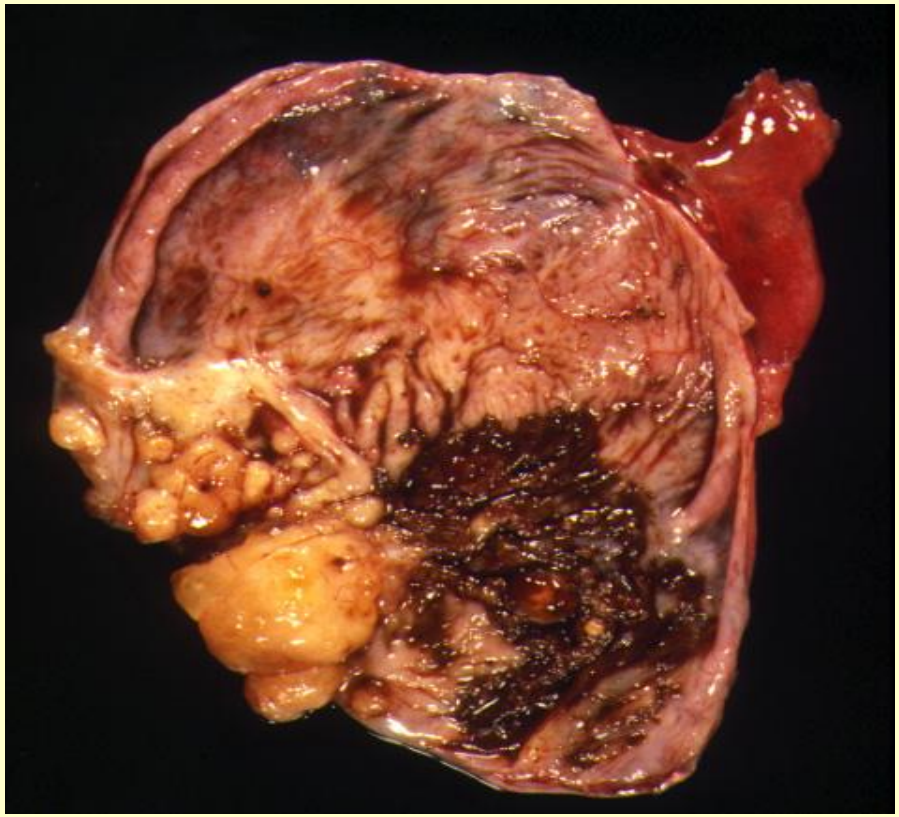
Beta-Catenin	20-40%
ARID1A	30%
PTEN	15-20%
PIK3CA	20%
MSI	15%
K-RAS	4-35%
TP53	10%

Classification of Gyn Cancers based on Origin and Mutations

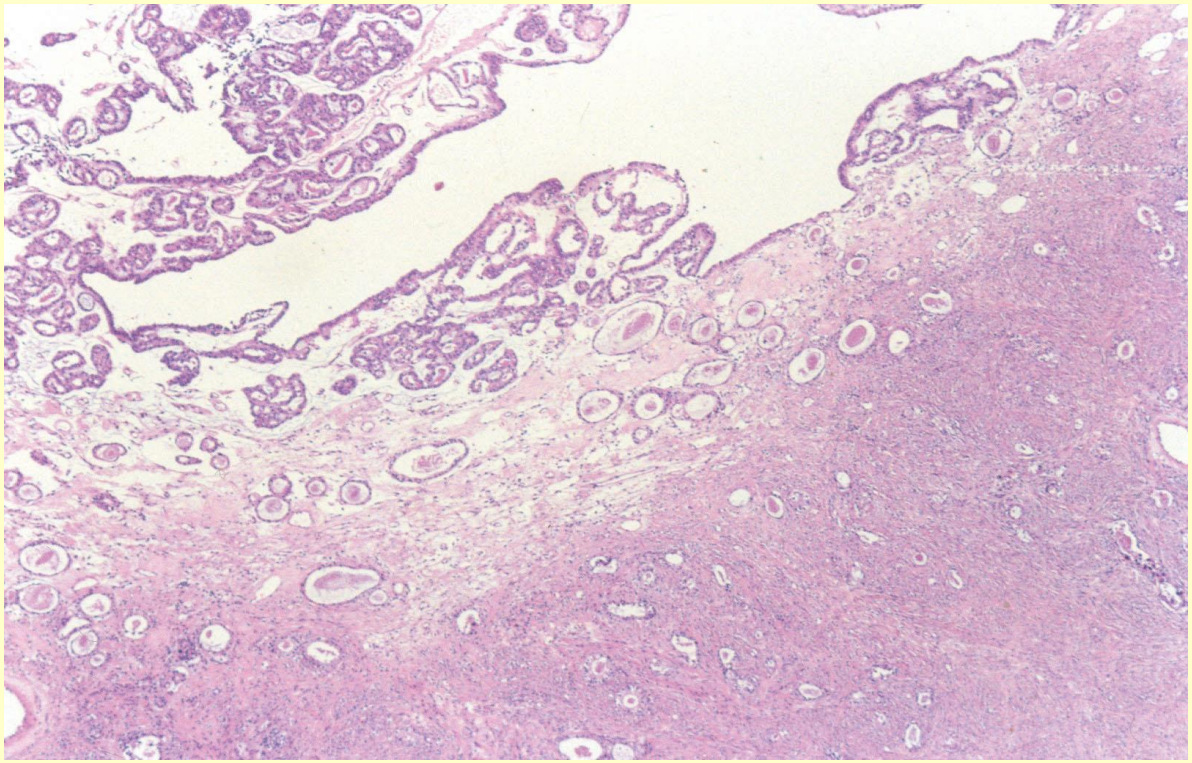


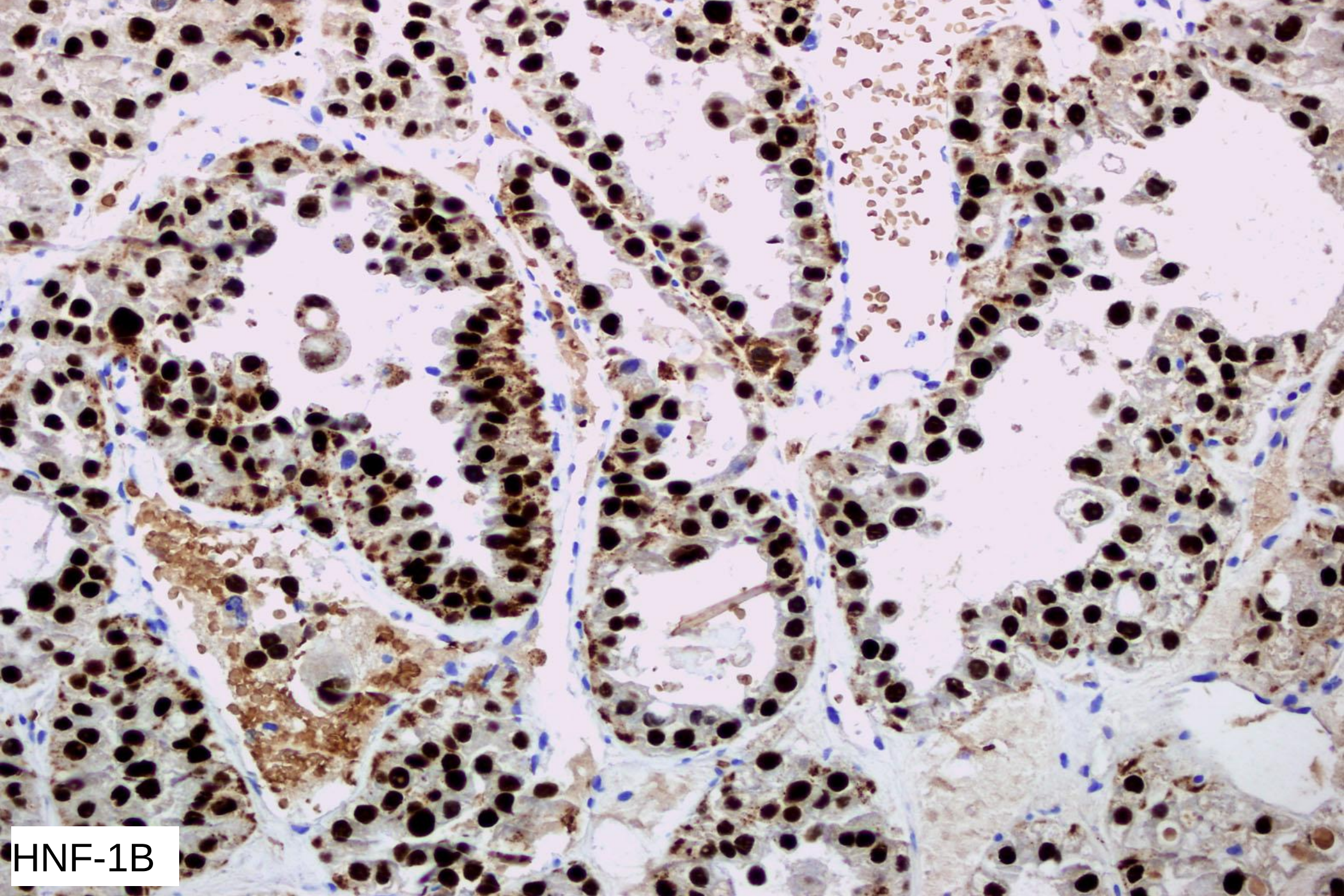
Clear Cell Carcinoma

Endometriotic Chocolate Cyst

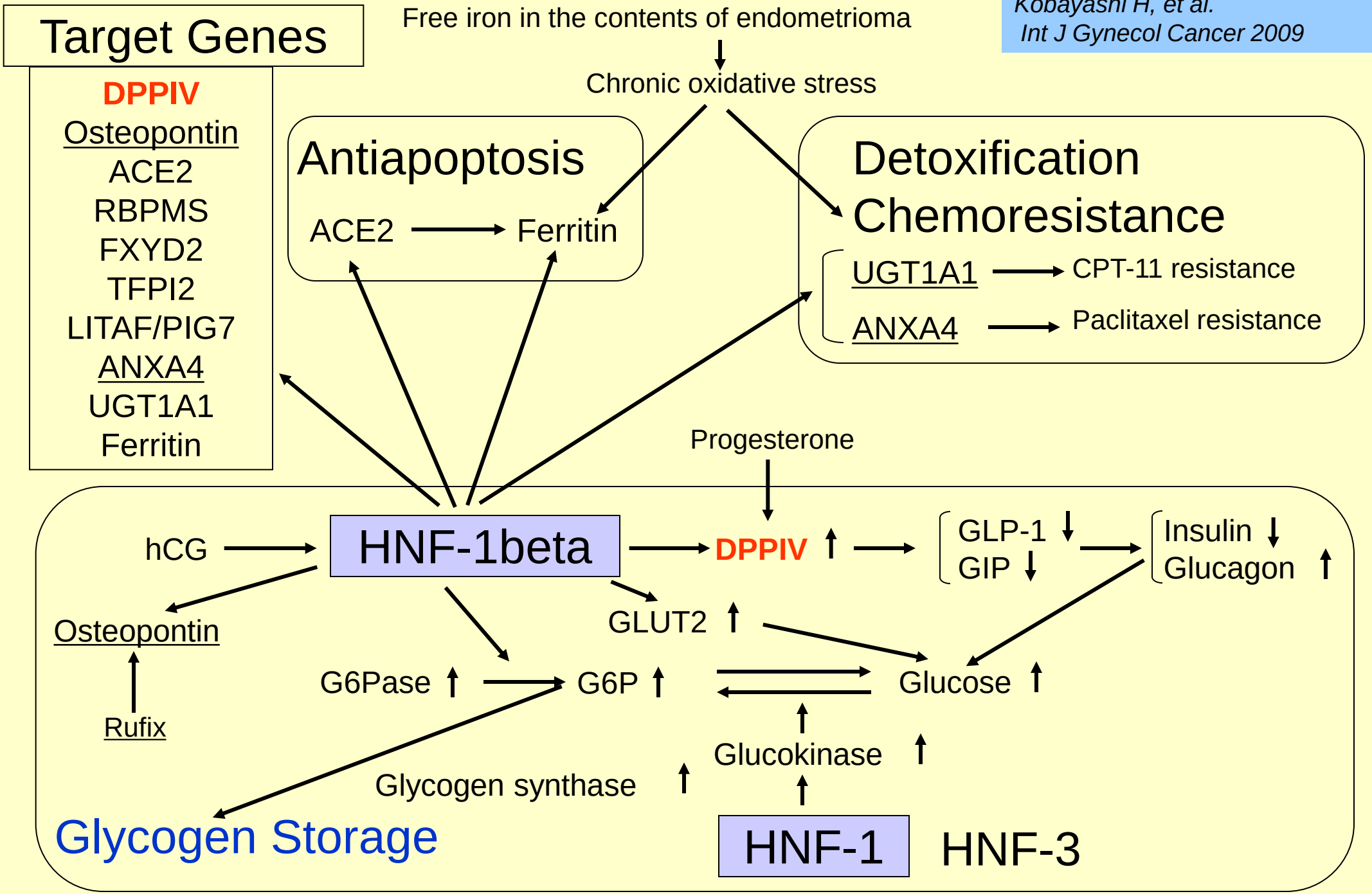


Adenofibroma




HNF-1B

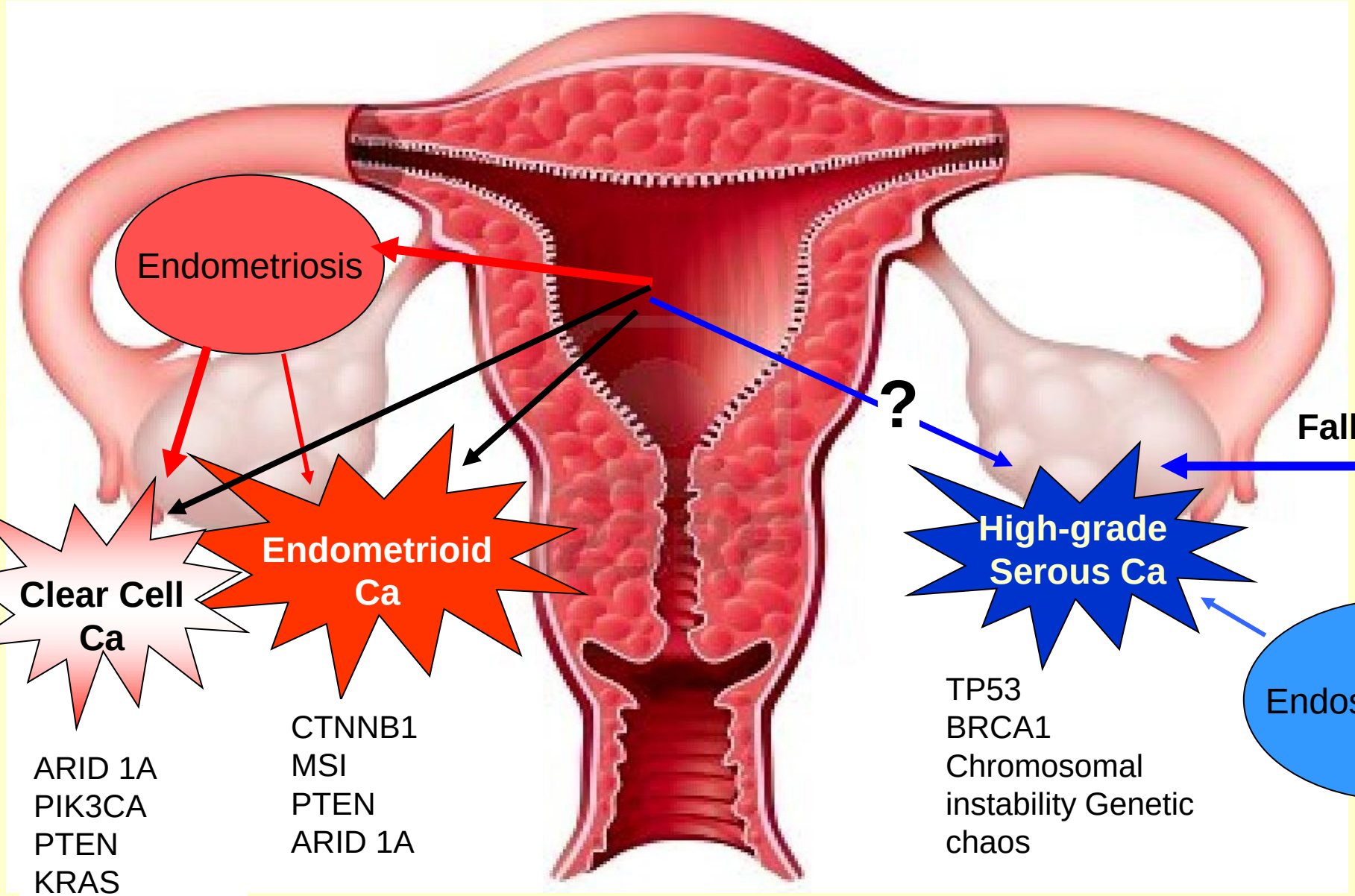
Kobayashi H, et al.
Int J Gynecol Cancer 2009



Molecular Genetic Alterations in Clear Cell Carcinomas of Ovary

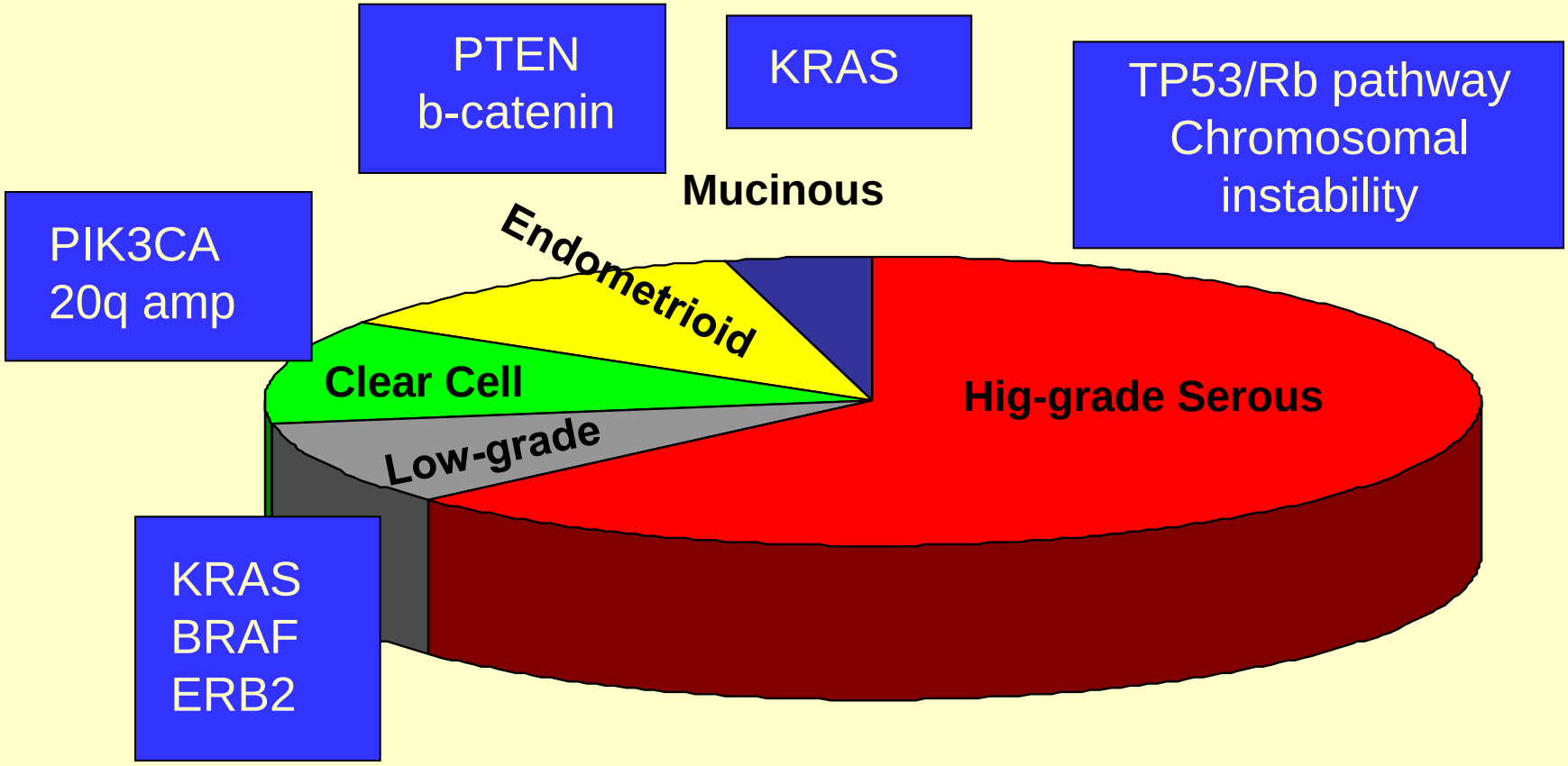
ARID1A	46%
PIK3CA	33%
K-RAS	15-30%
C-Met	22%
Her-2	10%
PPMD1D	10%
PTEN	5%
b-Catenin	5%
TP53	5%

Classification of Gyn Cancers based on Origin and Mutations



The five most common types of ovarian carcinoma

	High-grade serous	Clear cell	Endometrioid	Mucinous	Low-grade serous
Usual stage at diagnosis	Advanced	Early	Early	Early	Early or advanced
Presumed tissue of origin /precursor lesion	Fallopian tube or tubal metaplasia in inclusions of OSE	Endometriosis, adenofibroma	Endometriosis, adenofibroma	Adenoma–borderline – carcinoma sequence; teratoma	Serous borderline tumor
Genetic risk	BRCA1/2	?	HNPCC	?	?
Significant molecular abnormalities	p53 and pRb pathway	HNF-1β ARID1A	PTEN, β-Catenin, K-ras MI, ARID1A	K-ras	BRAF or K-ras
Proliferation	High	Low	Low	Intermediate	Low
Response to primary chemotherapy	80%	15%	?	15%	26-28%
Prognosis	Poor	Intermediate	Favorable	Favorable	Favorable


PTEN
b-catenin
KRAS
TP53/Rb pathway
Chromosomal
instability
Mucinous
PIK3CA
20q amp
Endometrioid
Clear Cell
Low-grade
Hig-grade Serous
KRAS
BRAF
ERB2

Thank you
for your
attention