



THE UNIVERSITY *of* EDINBURGH

Epithelial Ovarian Tumours

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Outline

- The classification of ovarian tumours
- The influence of molecular pathology on ovarian carcinoma classification
- Epithelial ovarian tumours
 - High grade serous carcinoma
 - Low grade serous carcinoma
 - Endometrioid carcinoma
 - Clear cell carcinoma
 - Mucinous carcinoma
 - Mixed tumours and rare entities
- Future directions

Ovarian tumours

(Tumours involving the ovary)

	Cell of origin	Type	Proportion (%)
Primary Epithelial	Not entirely clear. The different histological types have different origins and arise through different molecular pathways	High-grade serous Low-grade serous Endometrioid/clear cell Seromucinous Mucinous Brenner Carcinosarcoma Undifferentiated	65–70
Germ cell tumours	Germ cells	Teratoma Dysgerminoma Yolk sac tumour Embryonal carcinoma	15–20
Sex cord/stromal tumours	Ovarian sex cords and stroma	Granulosa cell tumours Thecoma/fibroma Sertoli–Leydig tumours	5–10
Miscellaneous	Various	e.g. Lymphoma	
Secondary Metastases	-	-	5-10

Clinical Patterns of Disease



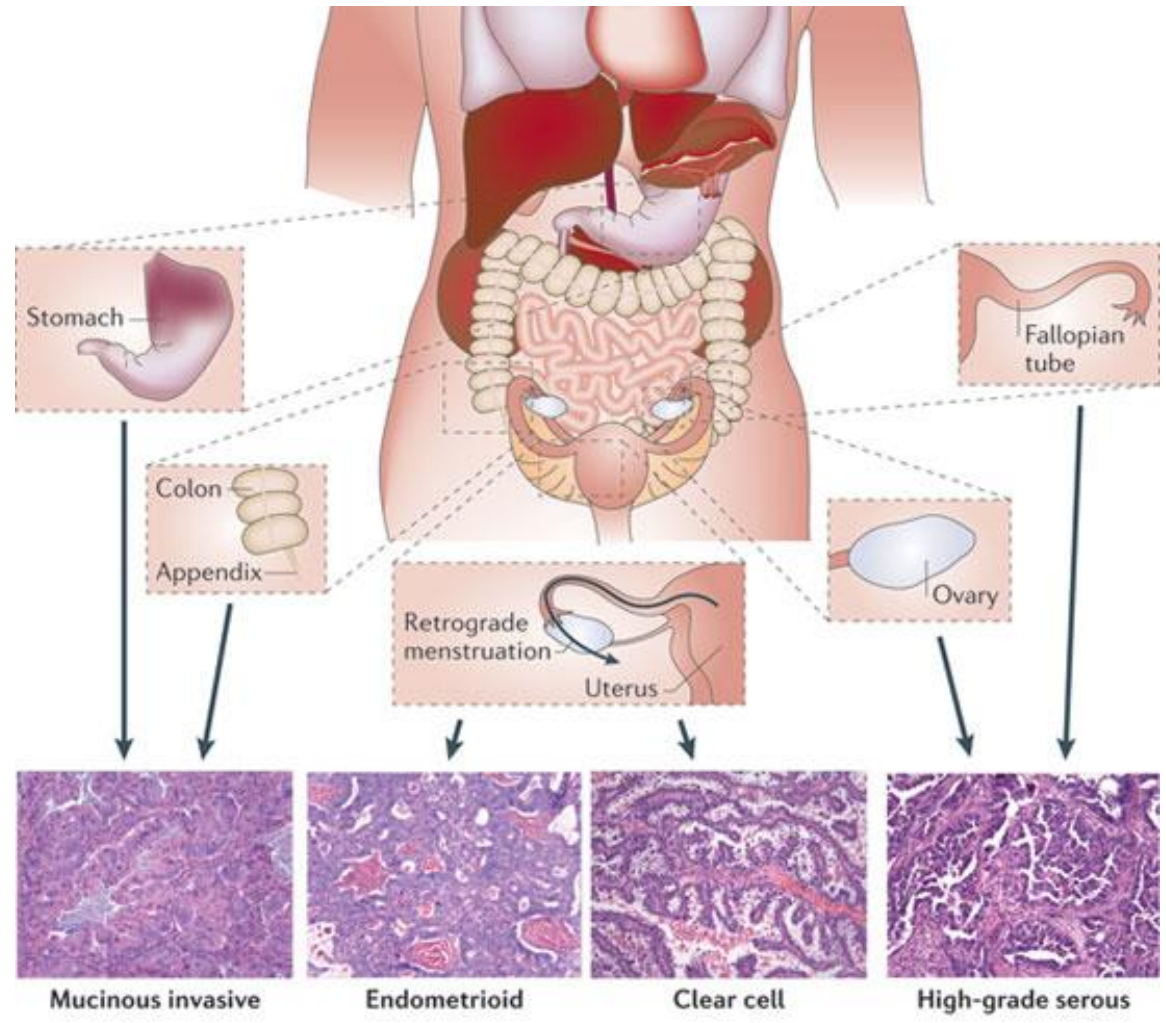
Circumscribed Smooth-surfaced Cystic Tumour



Disseminated Intra-abdominal Disease



Ovarian Metastasis



Nature Reviews | [Cancer](#)

Vaughan et al Nat Rev Cancer 2011; 11: 719-725

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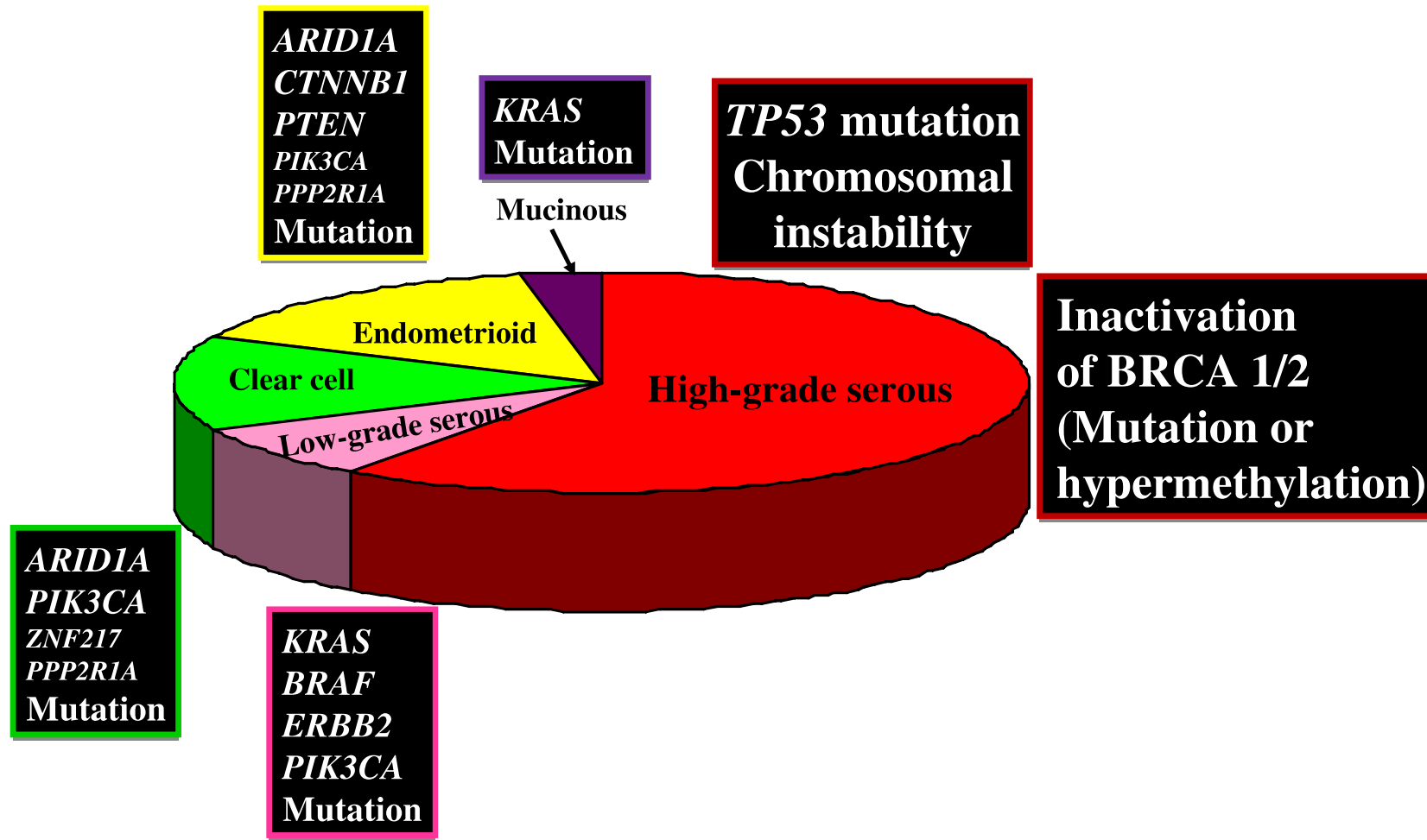
Ovarian Epithelial Tumours

	Serous	Endometrioid	Clear Cell	Mucinous	Transitional	Unclassified
Borderline/ AP						
Grade 1						
Grade 2						
Grade 3						

Ovarian Epithelial Tumours – Current Position

← Carcinosarcoma / undifferentiated carcinoma →

Origin	Fallopian Tube		Endometriosis			Unclear	
	High-Grade Serous	Low-Grade Serous	Endometrioid	Seromucinous	Clear cell	Mucinous	Brenner
Borderline /AP	Hatched	Magenta	Yellow	Grey	Green	Purple	Light Blue
Grade 1				Yellow			
Grade 2	Red	Hatched					
Grade 3	Red	Hatched					



Diagnostic Biomarkers

ORIGINAL ARTICLE

Diagnosis of Ovarian Carcinoma Cell Type is Highly Reproducible A Transcanadian Study

Martin Köbel, MD,* Steve E. Kalloger, BSc,† Patricia M. Baker, MD,‡
Carol A. Ewanowich, MD,§ Jocelyne Arseneau, MD,|| Viktor Zherebitskiy, MD,‡
Sorani Abdulkarim, MD,¶ Samuel Leung, MSc,† Máire A. Duggan, MD,* Dan Fontaine, MD,¶
Robin Parker, MD,# David G. Huntsman, MD,† and C. Blake Gilks, MD, FRCPC†

Am J Surg Pathol 2010; 34: 984-993

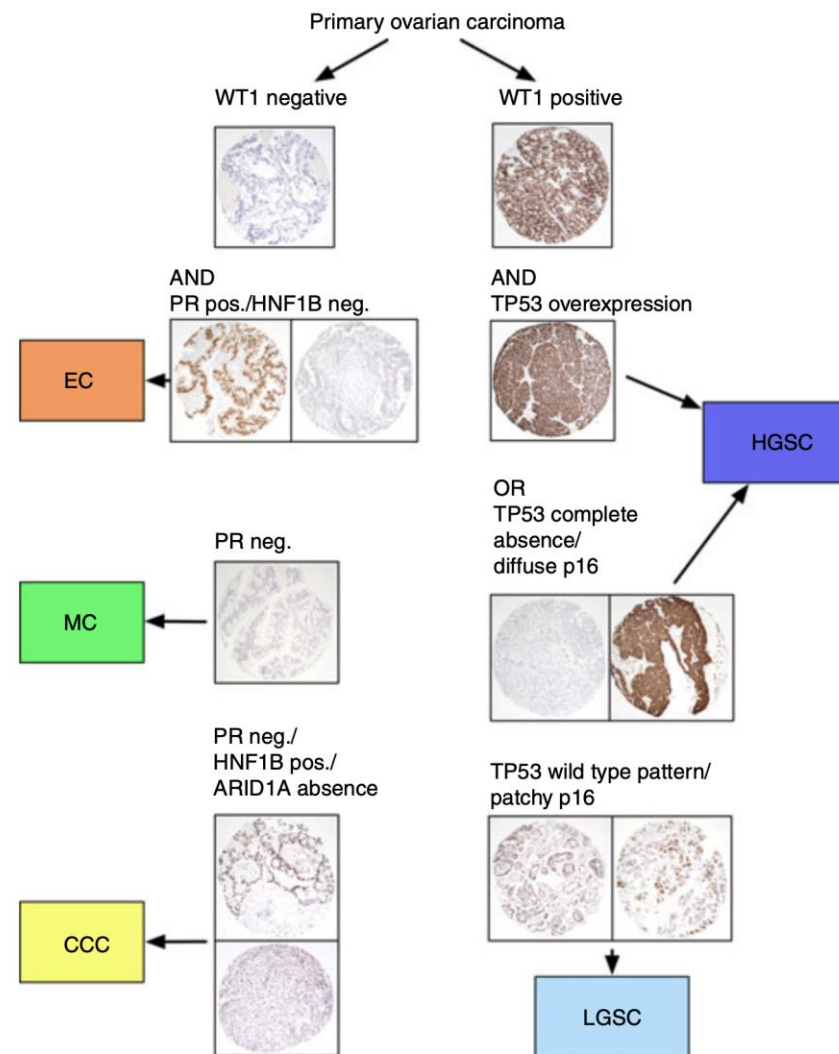
Histopathology



Histopathology 2014, 64, 1004–1013. DOI: 10.1111/his.12349

Ovarian carcinoma histotype determination is highly reproducible, and is improved through the use of immunohistochemistry

Martin Köbel, Julia Bak,¹ Björn I Bertelsen,² Olli Carpen,³ Anni Grove,⁴ Estrid S Hansen,⁵ Anne-Marie Levin Jakobsen,⁶ Marianne Lidang,⁷ Anna Måsbäck,⁸ Anna Tolf,⁹ C Blake Gilks¹⁰ & Joseph W Carlson¹¹

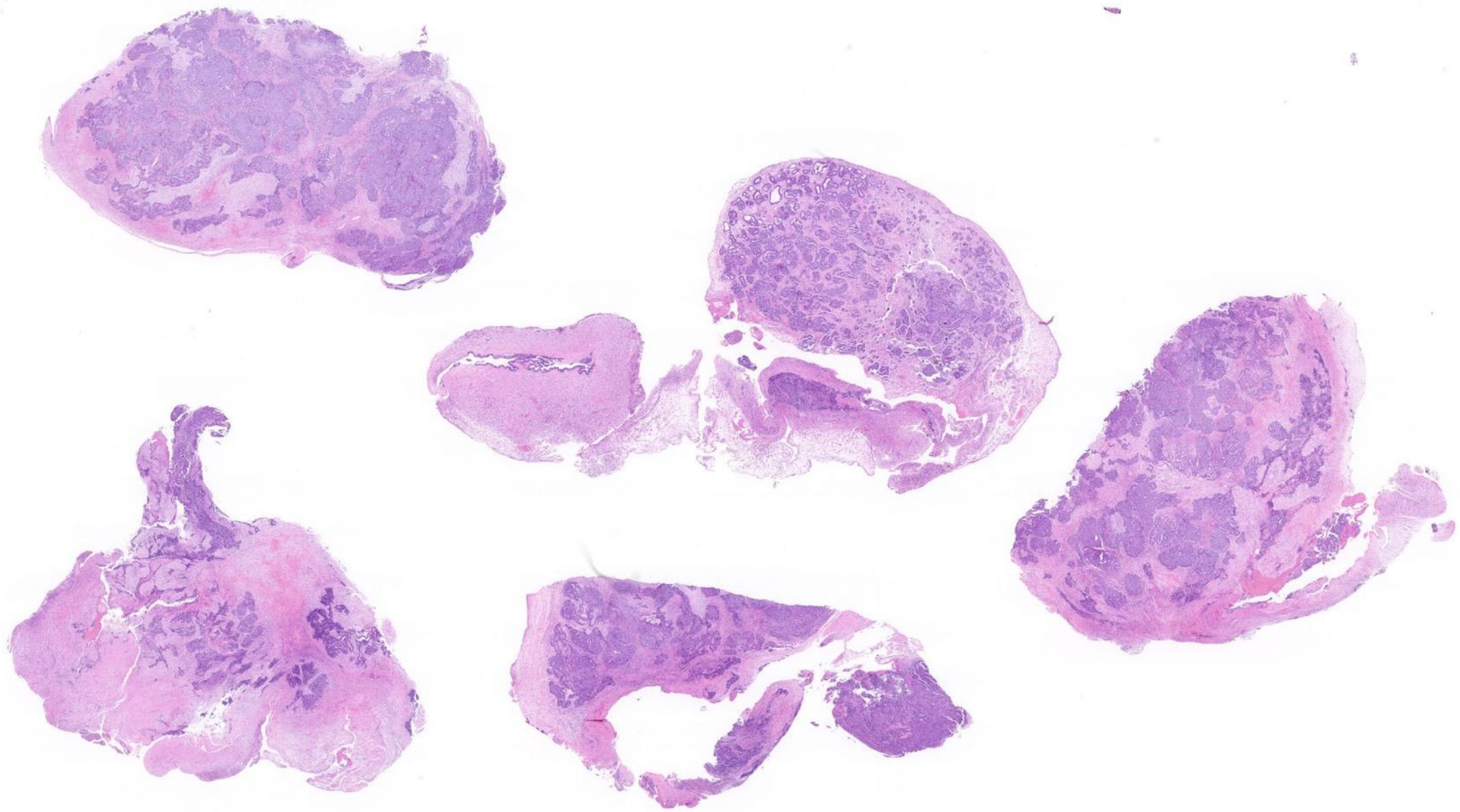


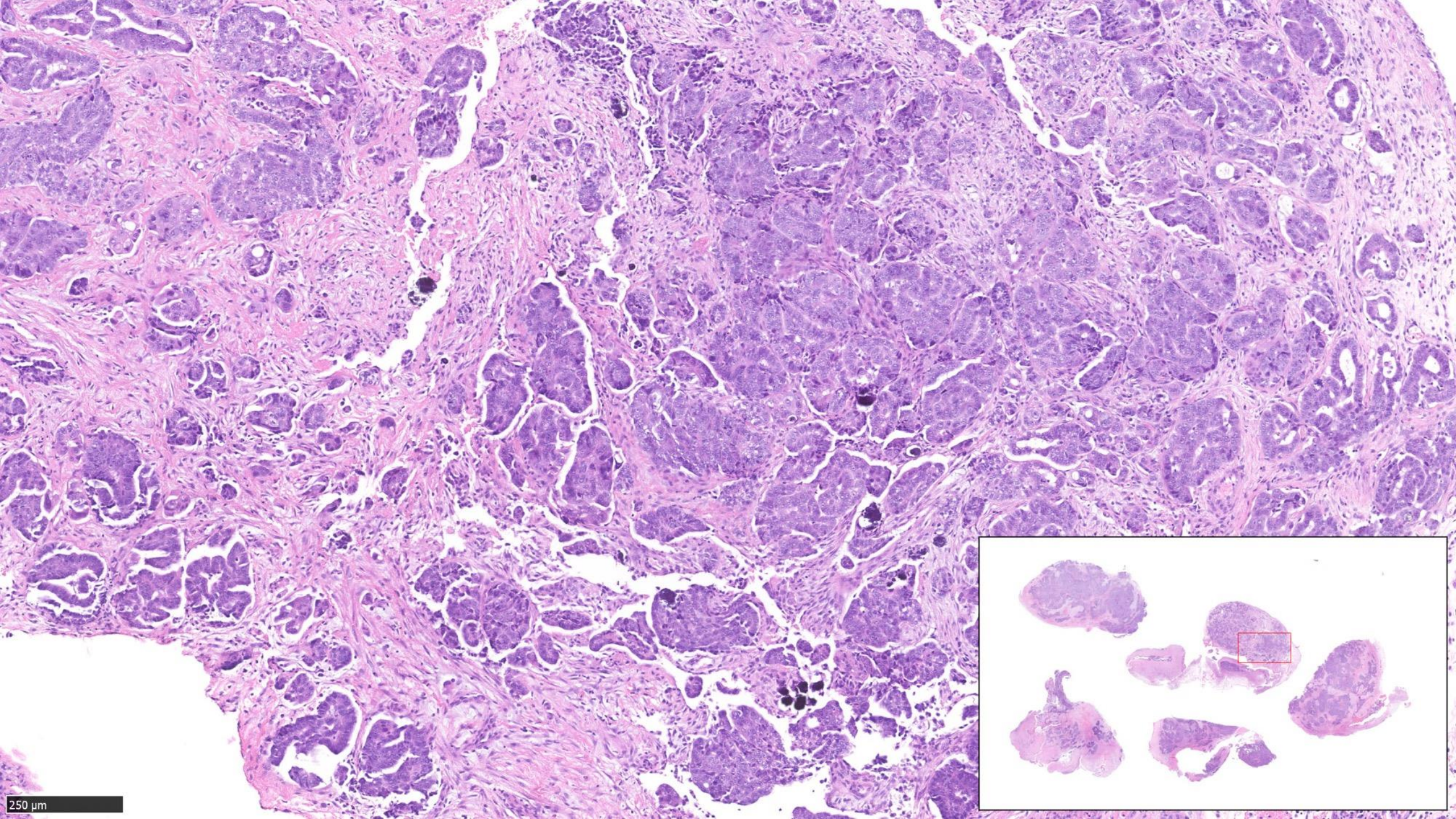
Ovarian Carcinoma Phenotypes

- High grade serous carcinoma – PAX8 positive, WT1 positive, p53 mutant (most commonly diffuse or null)
- Low grade serous carcinoma – PAX8 positive, WT1 positive, p53 wild type
- Endometrioid carcinoma – PAX8 positive, WT1 negative, ER/PR positive
 - Includes seromucinous carcinoma (WHO 2020)
- Clear cell carcinoma – PAX8 positive, WT1 negative, p53 wild type, ER/PR negative, napsin A positive, HNF1 β positive
- Mucinous carcinoma (excludes endometrioid carcinoma with mucinous differentiation)
 - Intestinal type carcinoma – PAX8 negative, WT1 negative, p53 variable, ER/PR negative

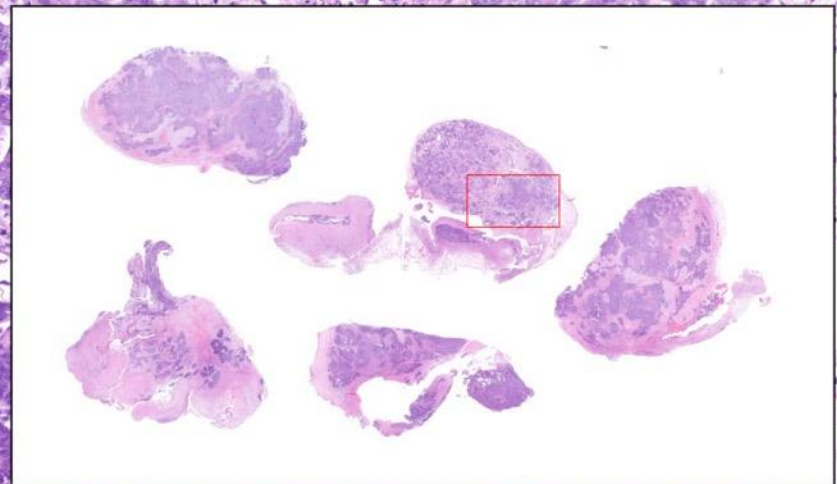
Outline

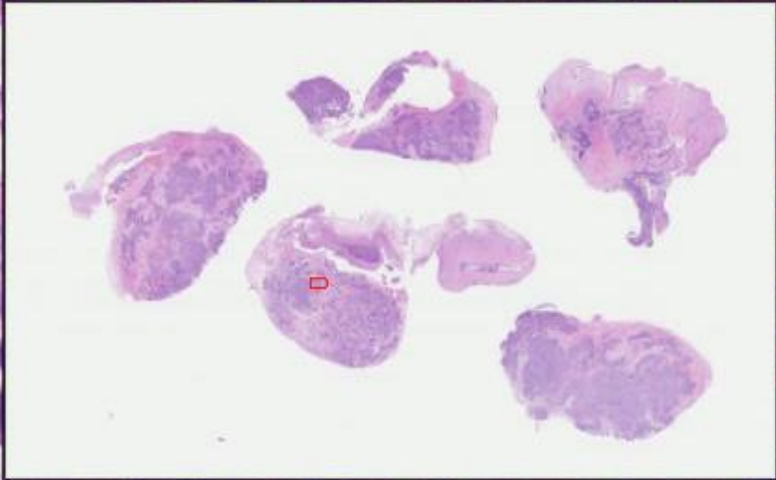
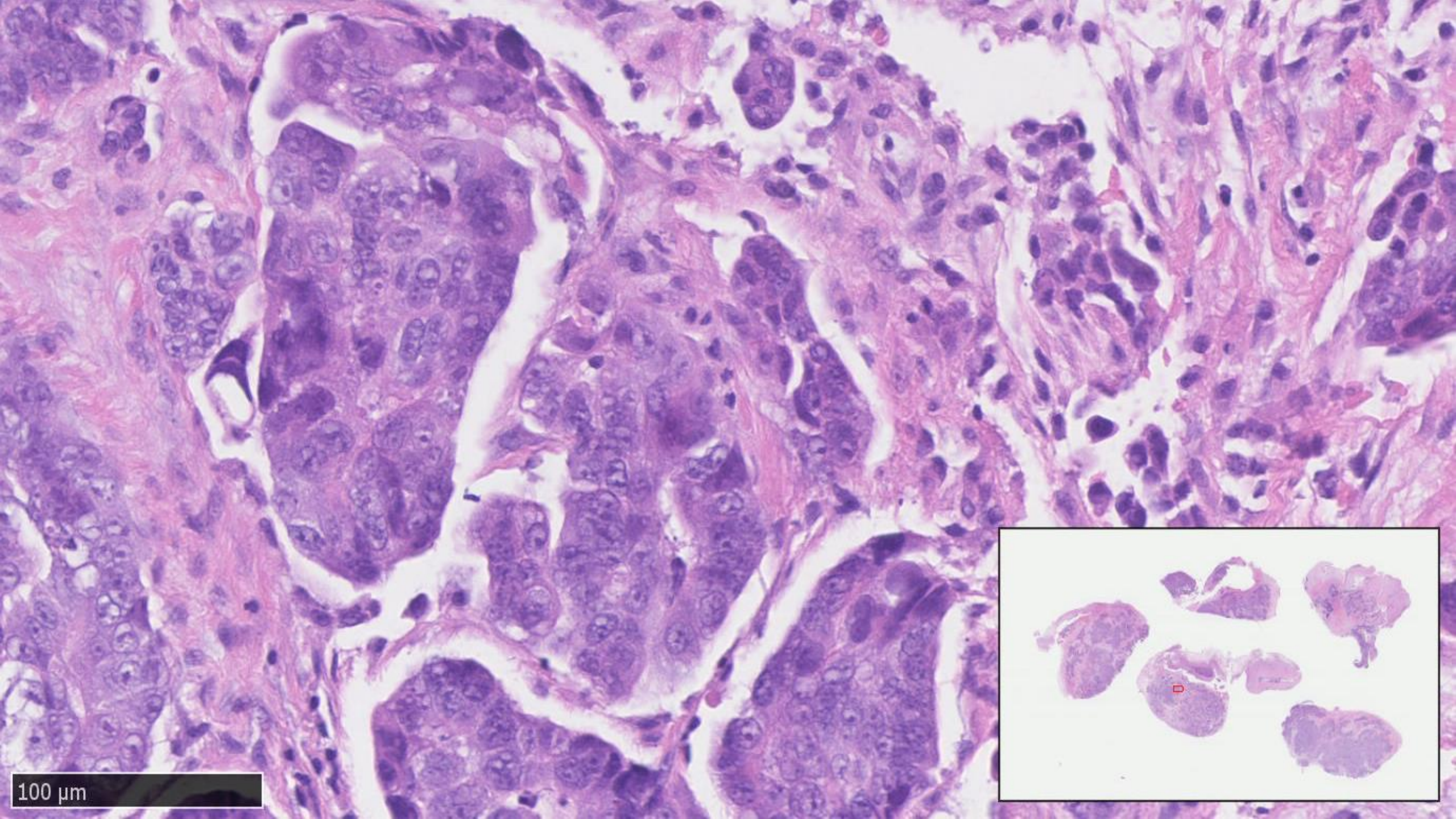
- The classification of ovarian tumours
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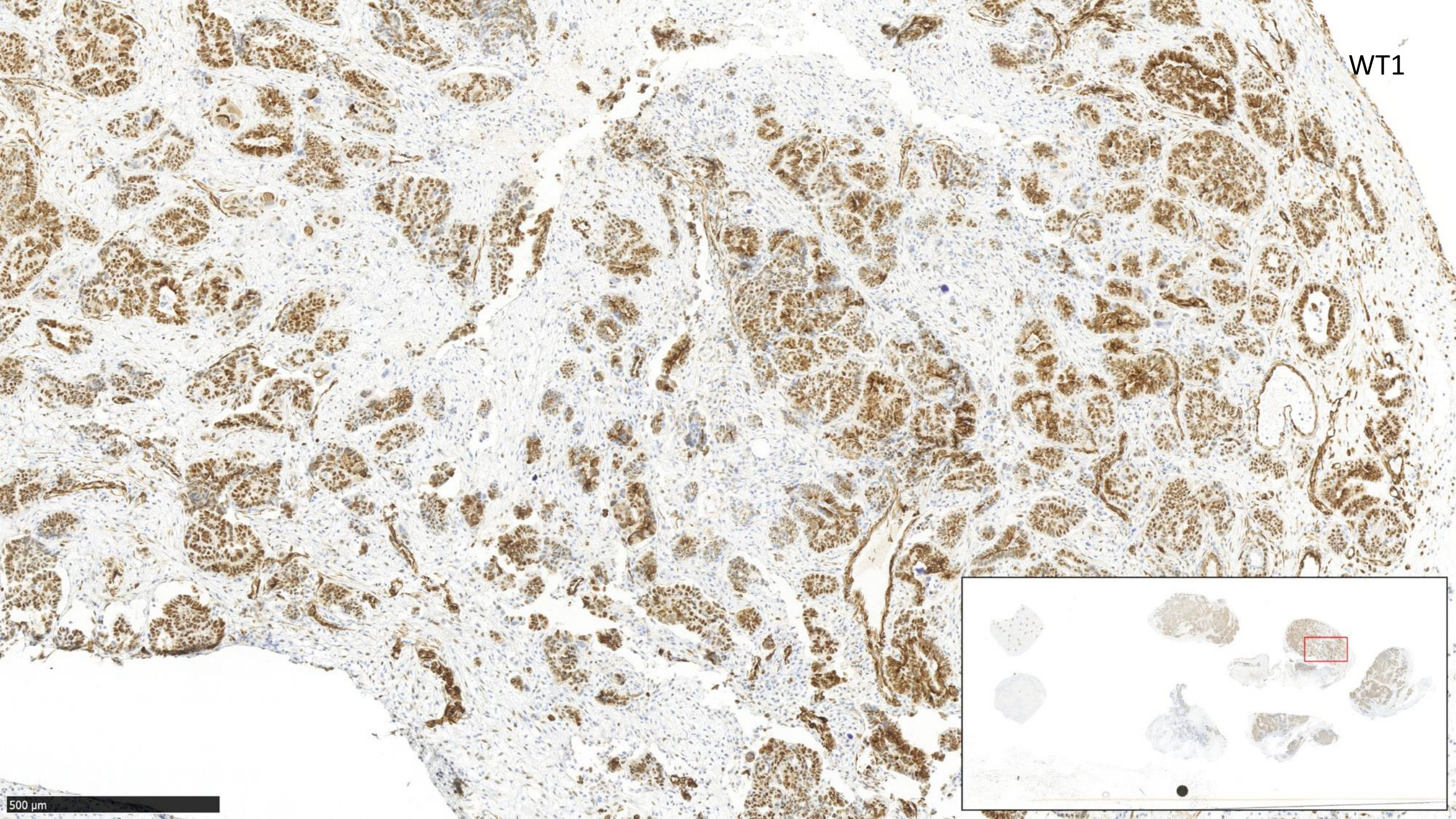
250 μ m





100 μ m

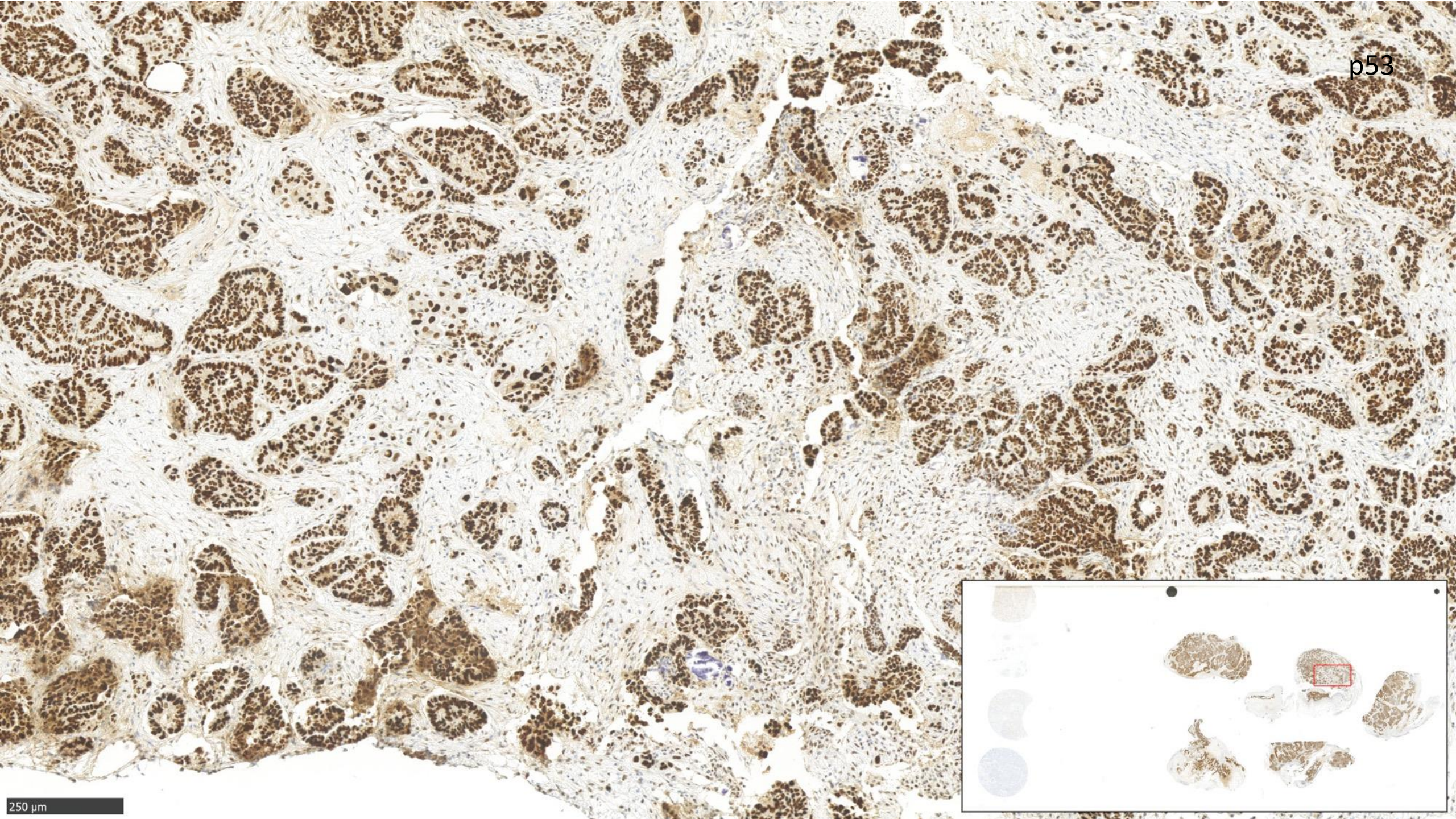
WT1



500 μm

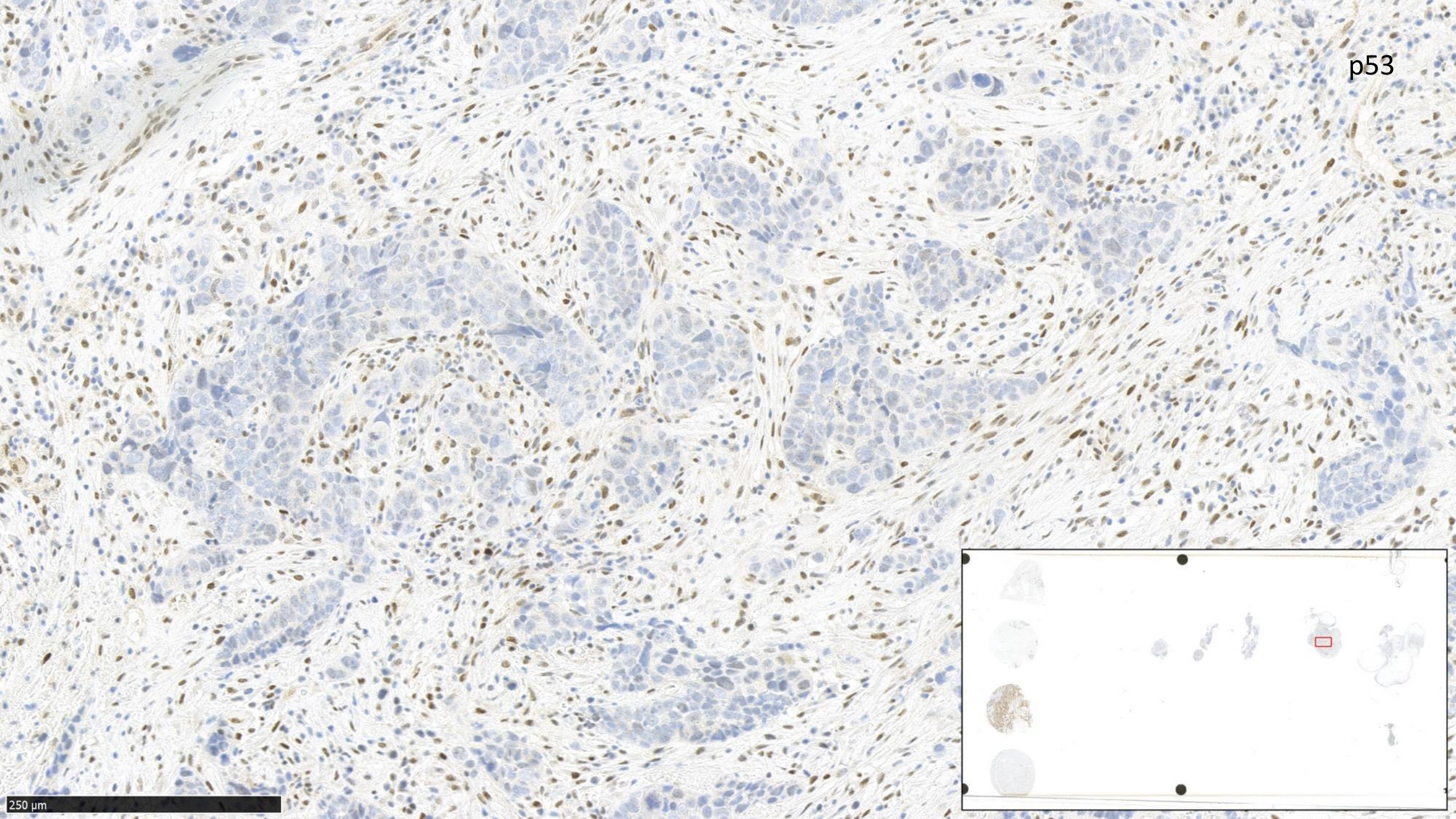


p53



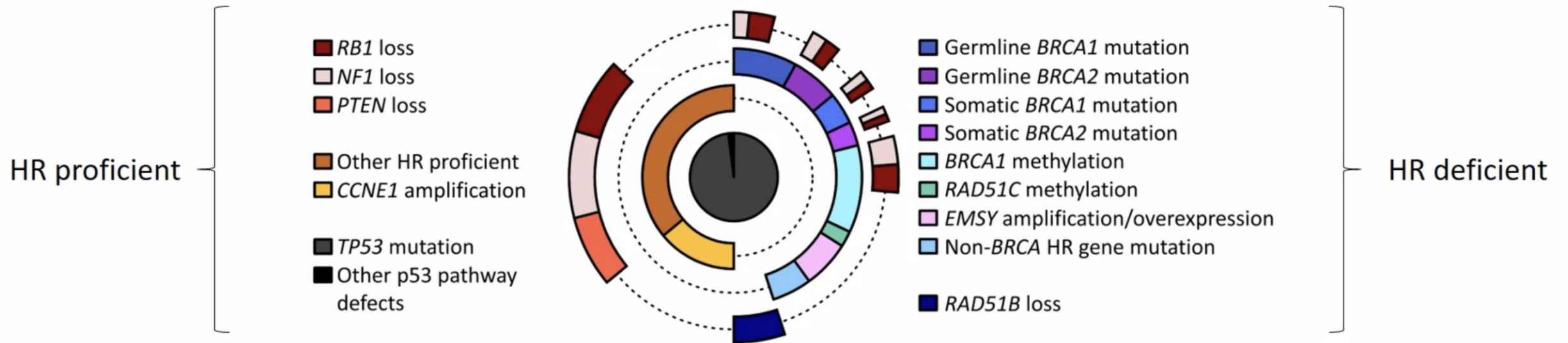
250 μm

p53

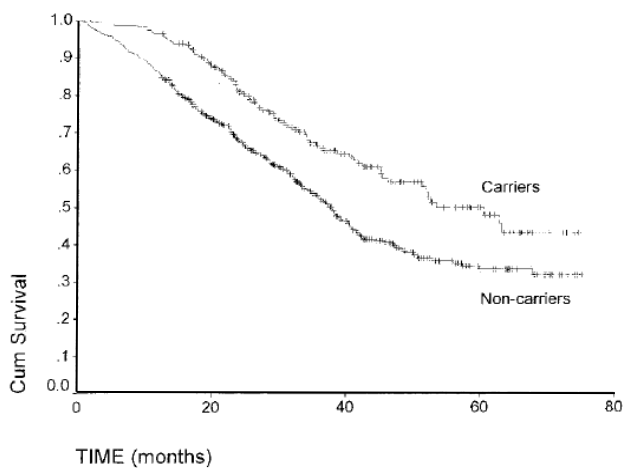
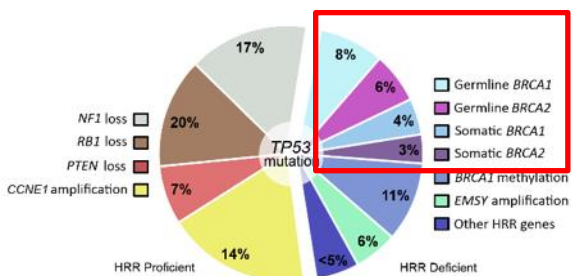


250 μm

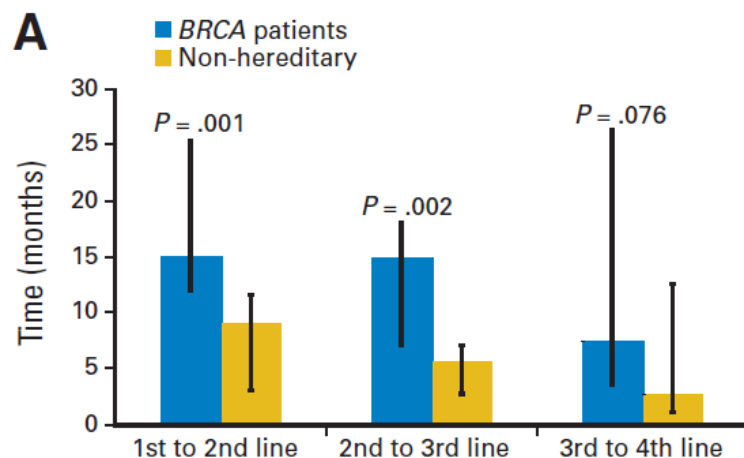
Genomic Features of High-grade Serous Ovarian Carcinoma



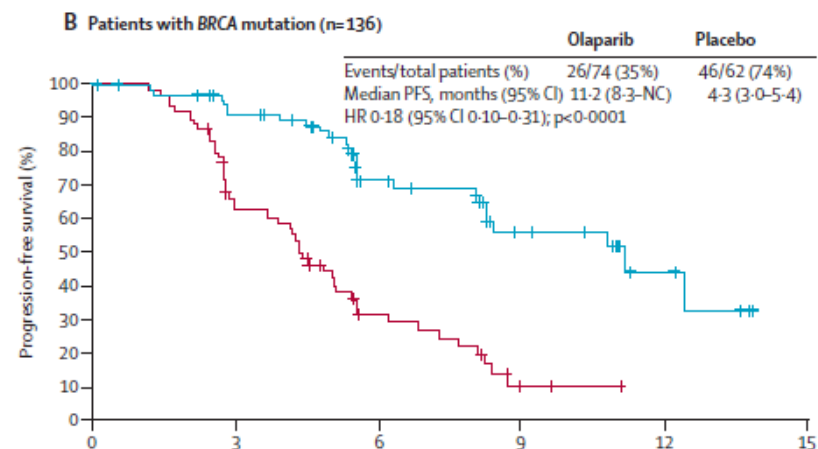
BRCA Mutant Ovarian Carcinoma - “BRCAness”



- Superior survival



- Superior response rate to multiple lines of platinum and prolonged platinum-free interval



- Sensitivity to PARP inhibitors

Ben David Y et al. J Clin Oncol 2002;20:463-6.

Tan DS et al. J Clin Oncol 2008;26:5530-6.

Ledermann J et al. Lancet Oncol 2014;15:852-61.

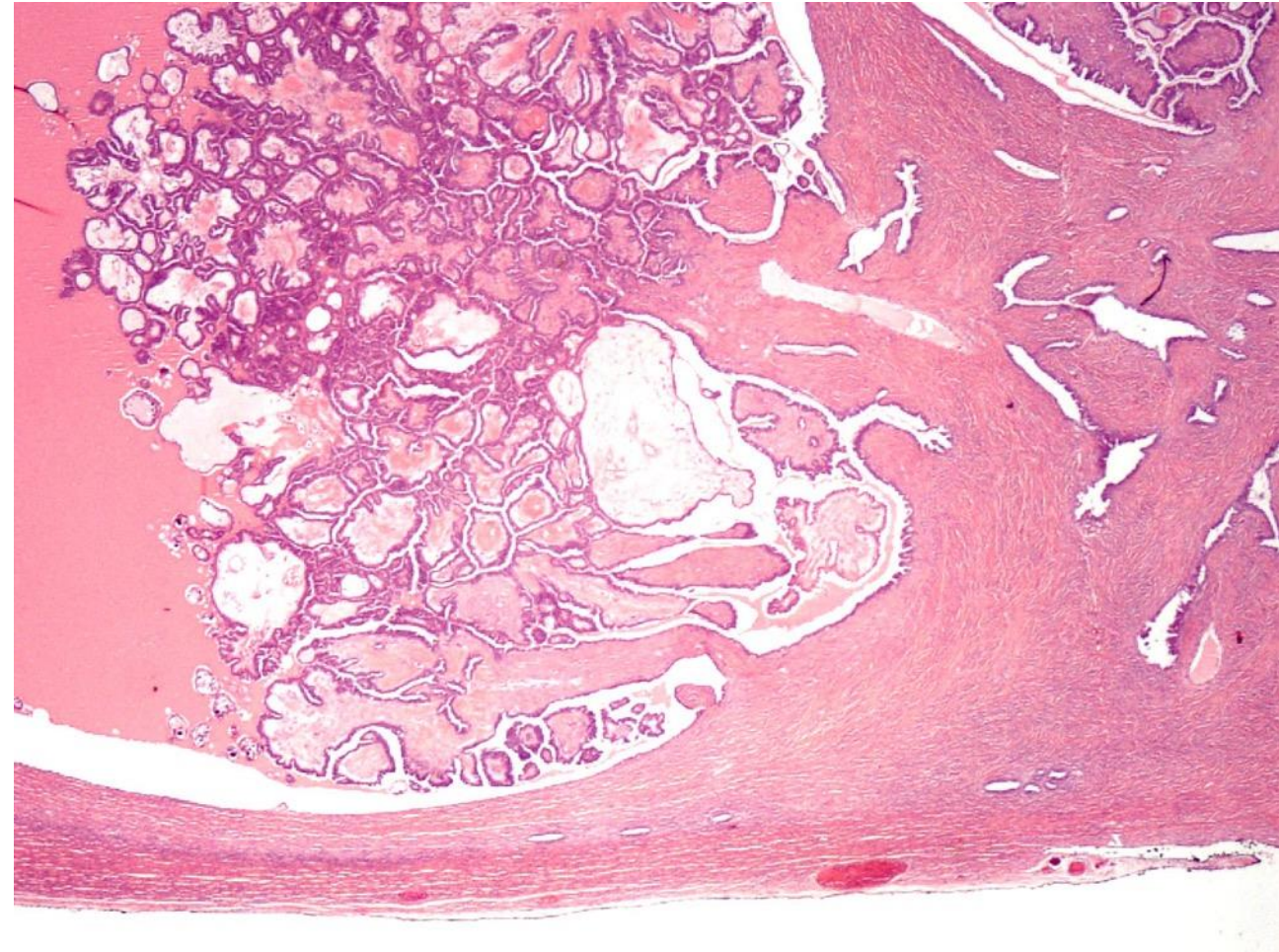
Moore et al. N Engl J Med 2018; 379: 2495-2505

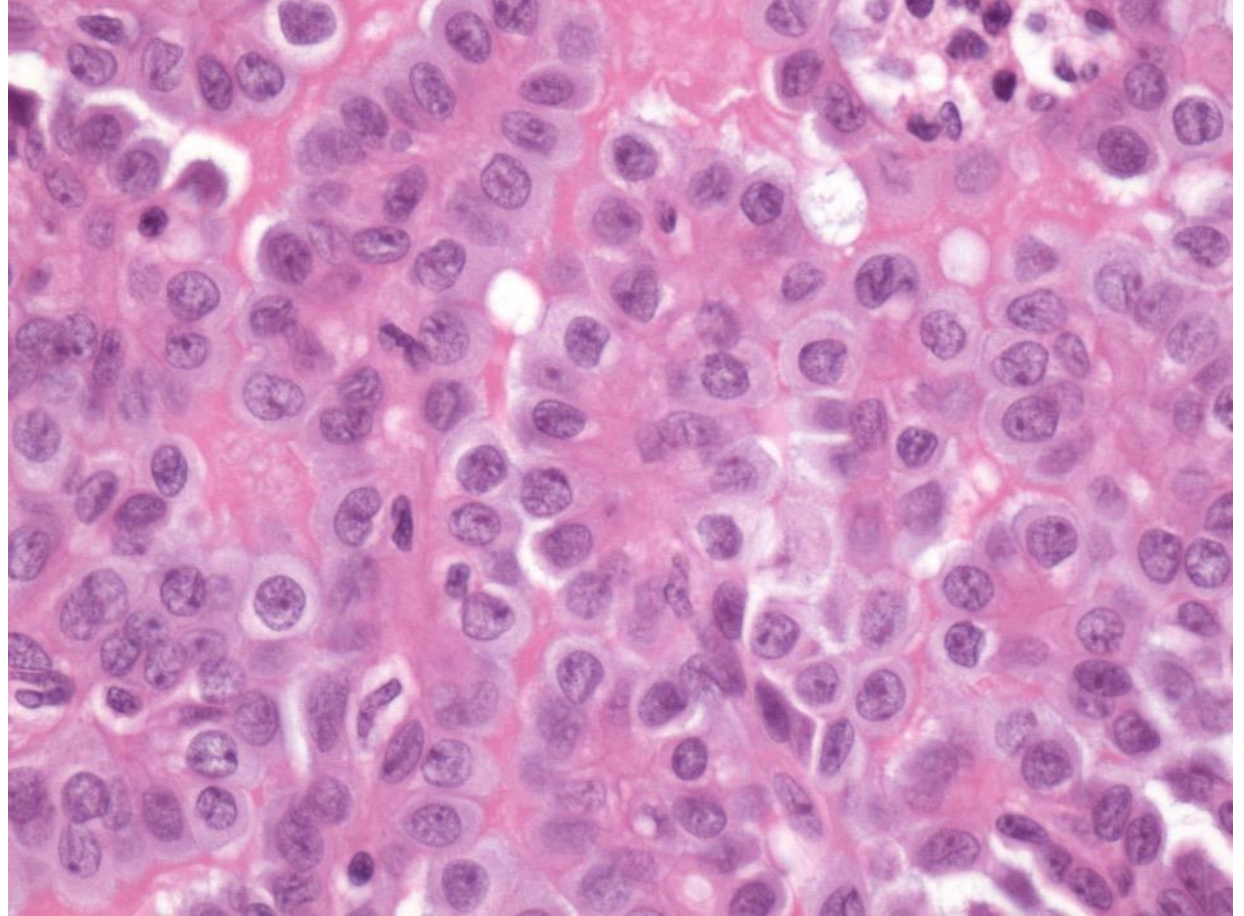
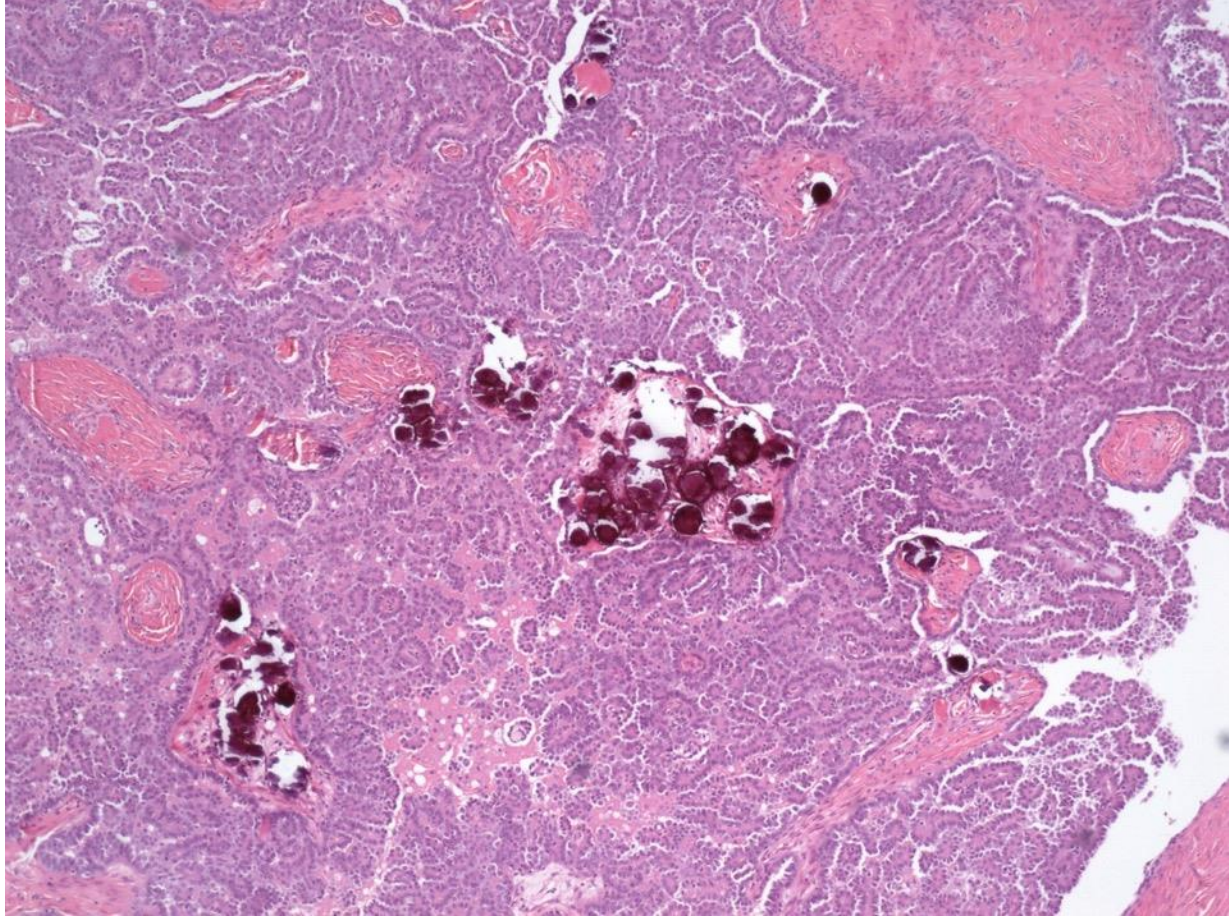
DiSilvestro et al. J Clin Oncol 2022; doi 10.1200/JCO.22.01549

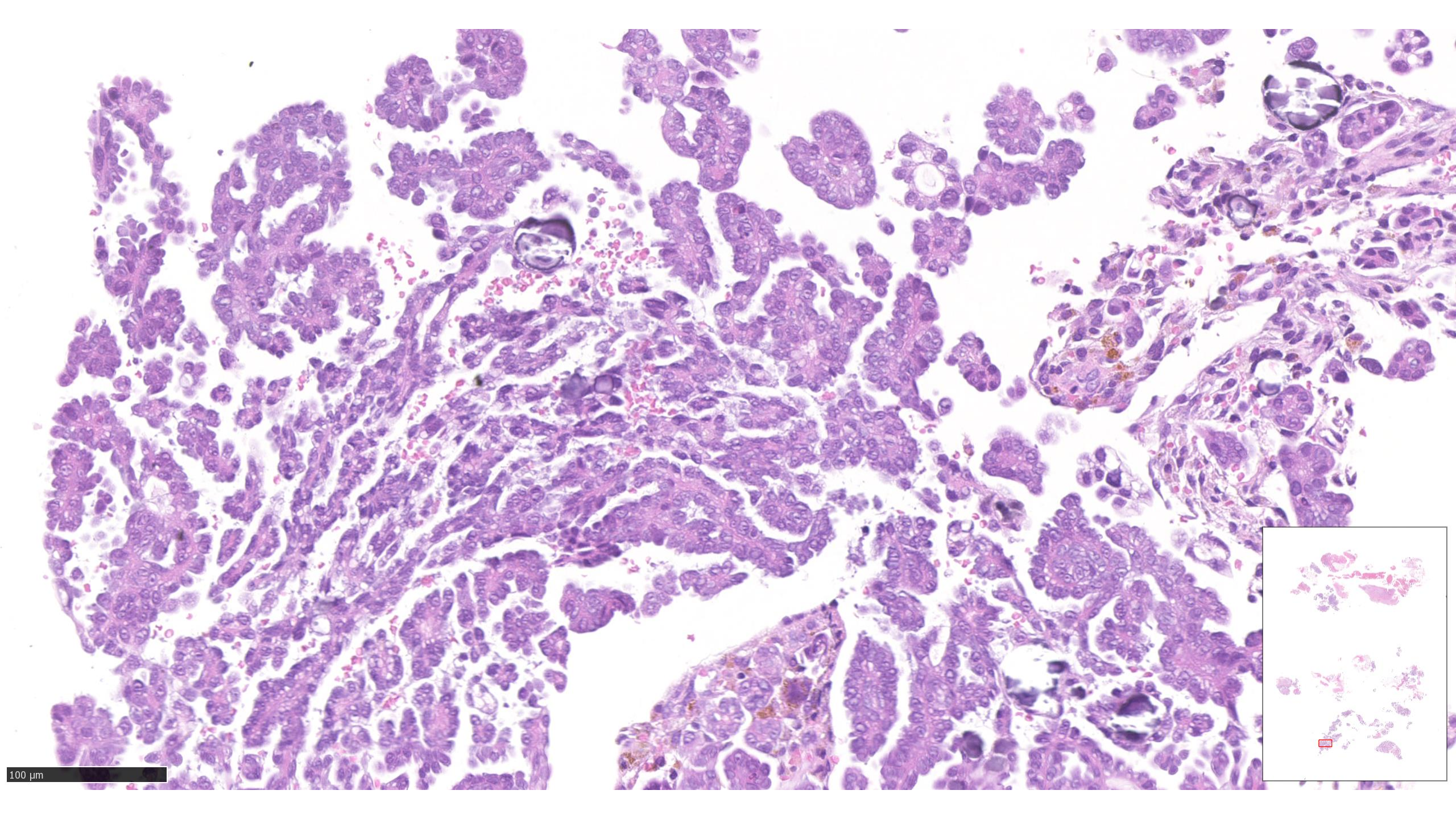
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Low-grade Serous Carcinoma

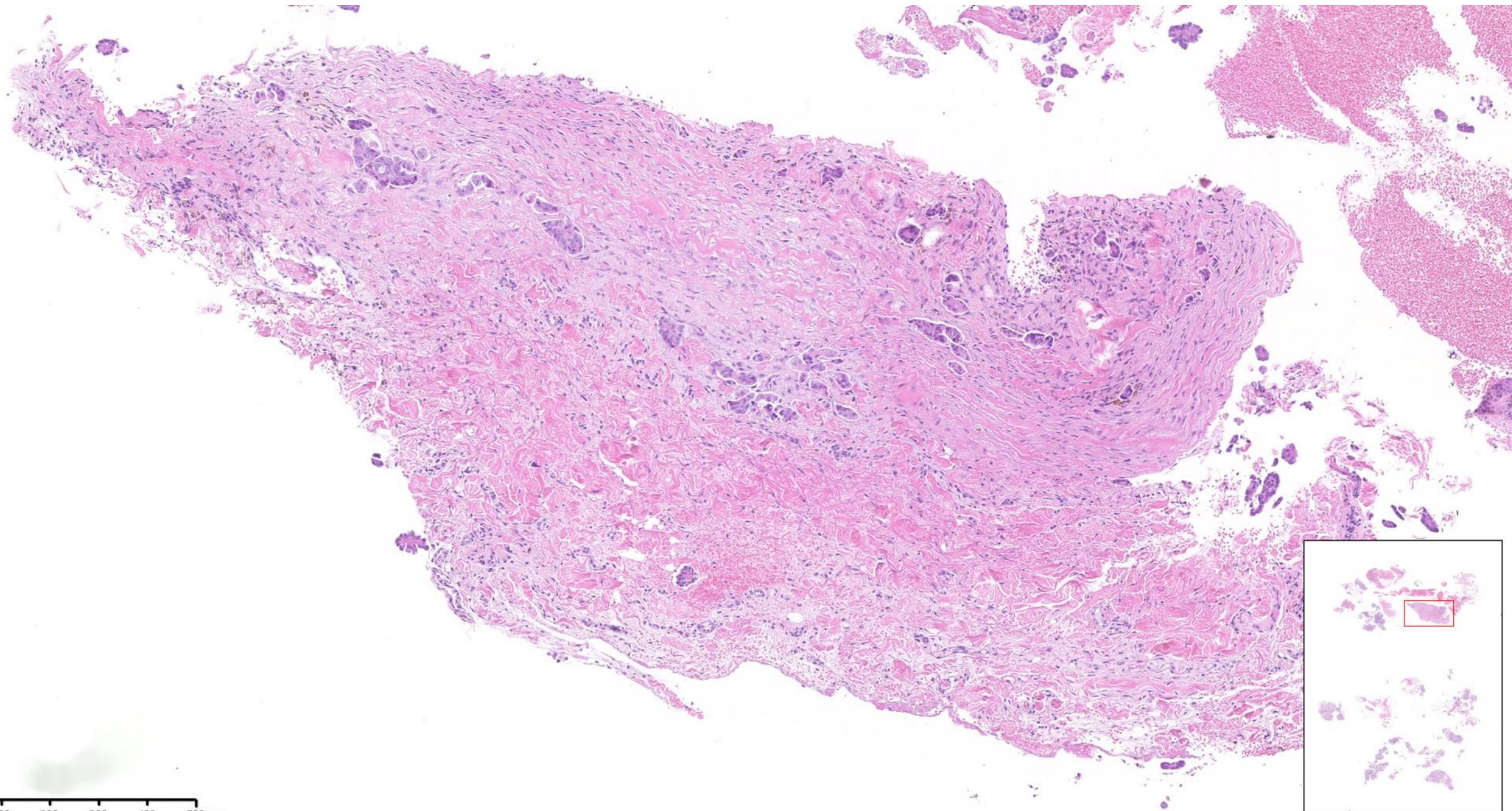






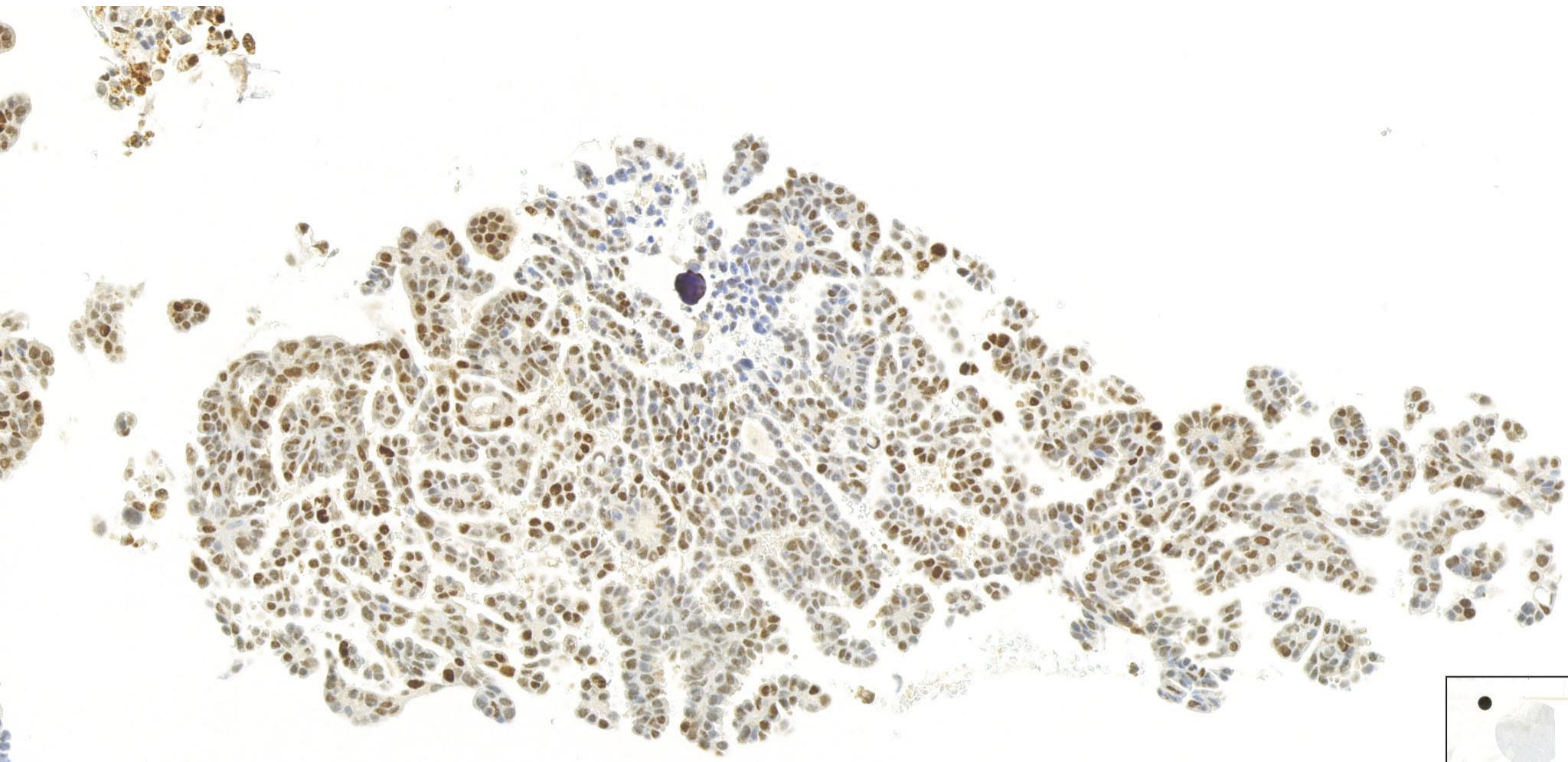
100 μ m





0 100 200 300 400 500 μm

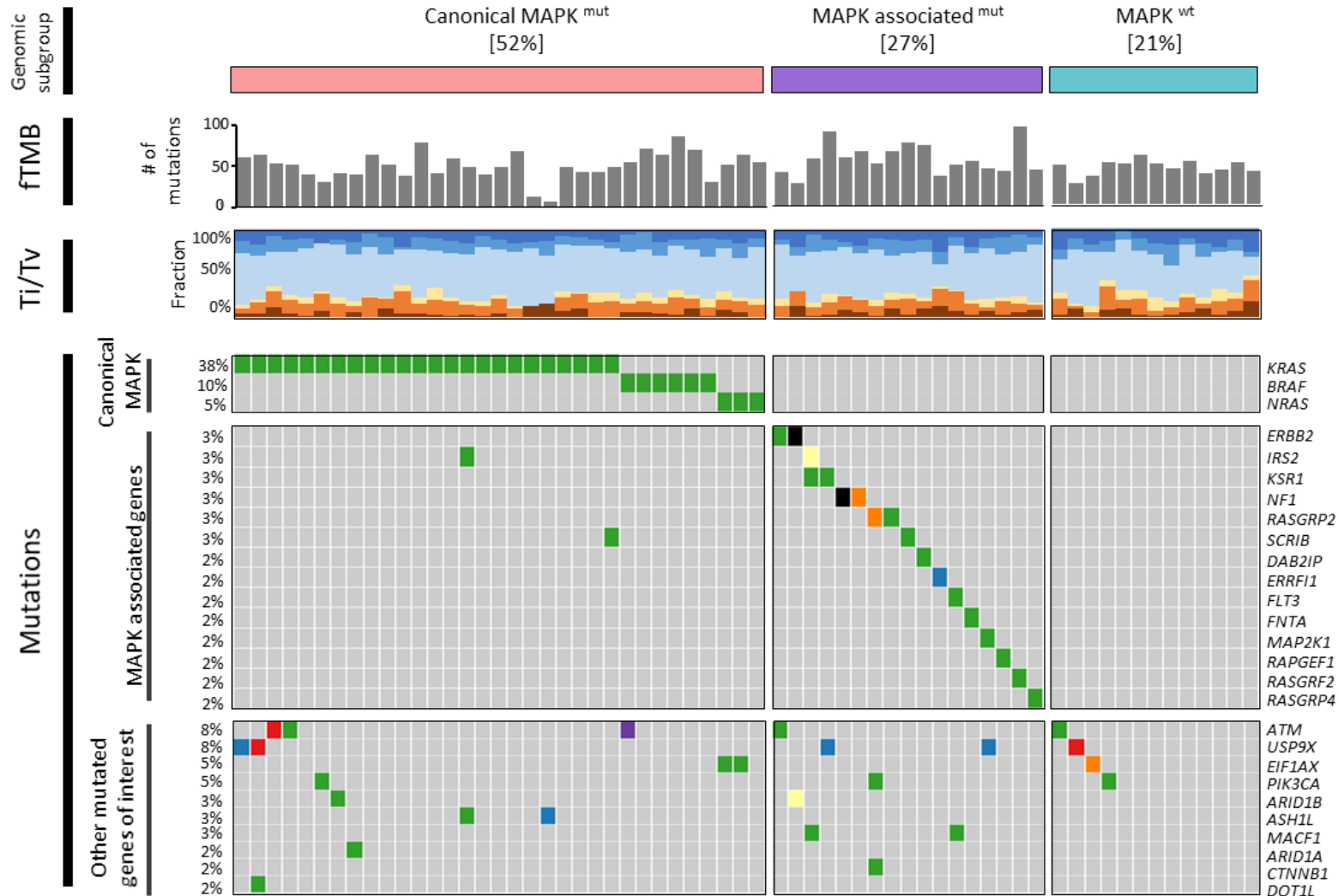
p53



0 50 100 150 200 250 μm



Low-grade Serous Carcinoma



- MAP kinase pathway and related mutations are common
 - *KRAS, BRAF, NRAS*
 - Others
- Pathway mutation may predict behaviour
- Evidence for efficacy of MEK inhibitor trametinib in recurrent disease - Gershenson et al, Lancet 2022; 399: 541-543

Unpublished

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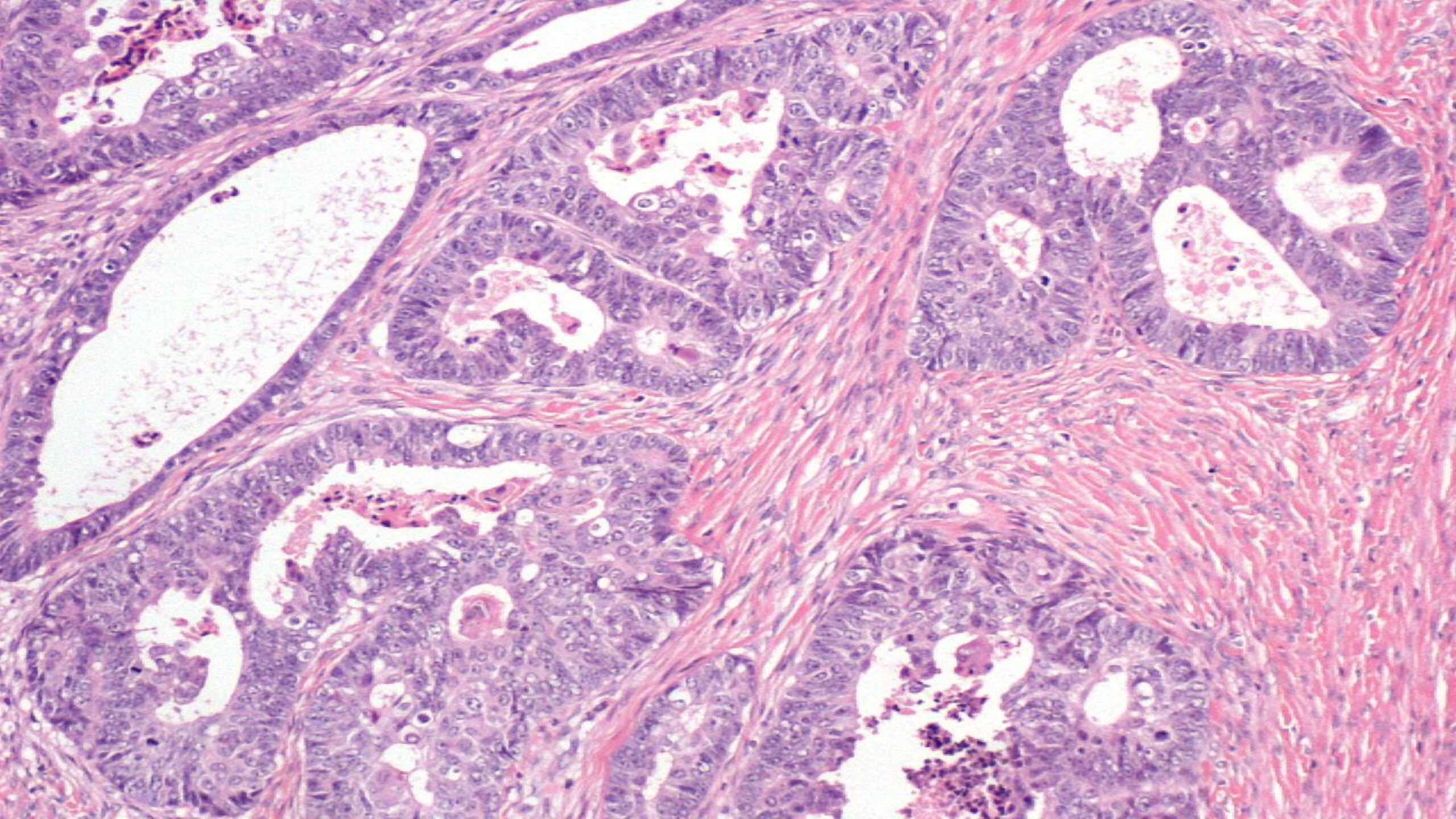
Ovarian Epithelial Tumours – Endometrioid Carcinoma

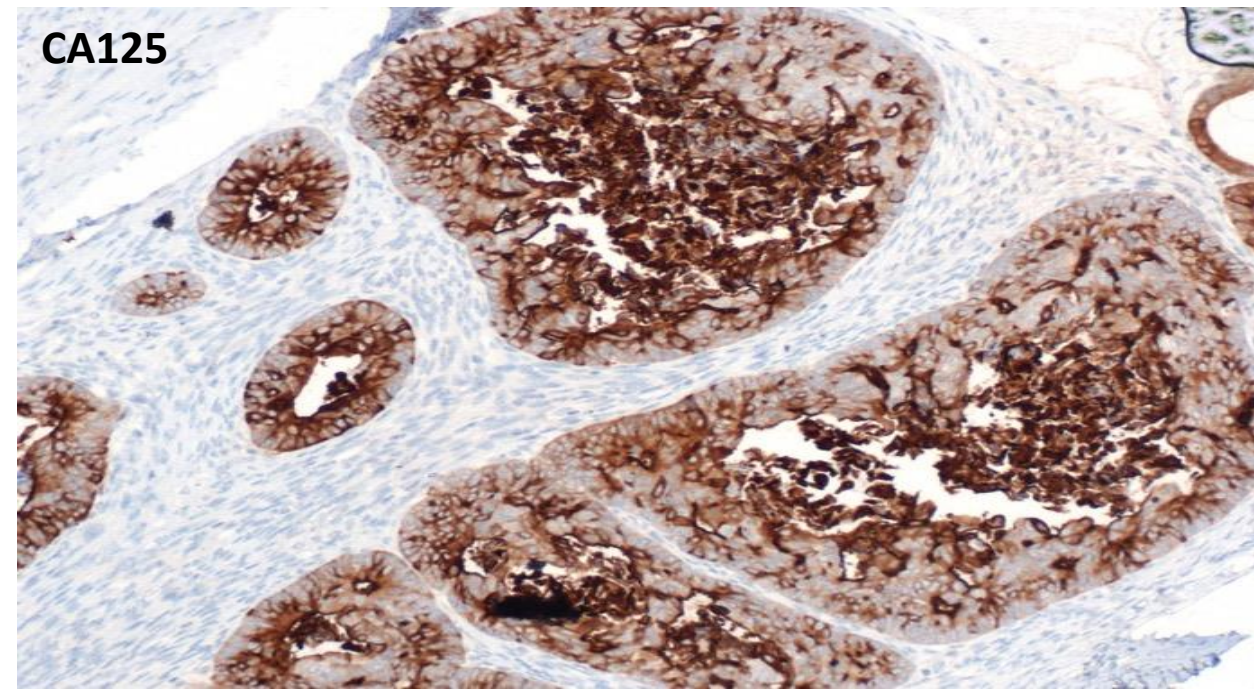
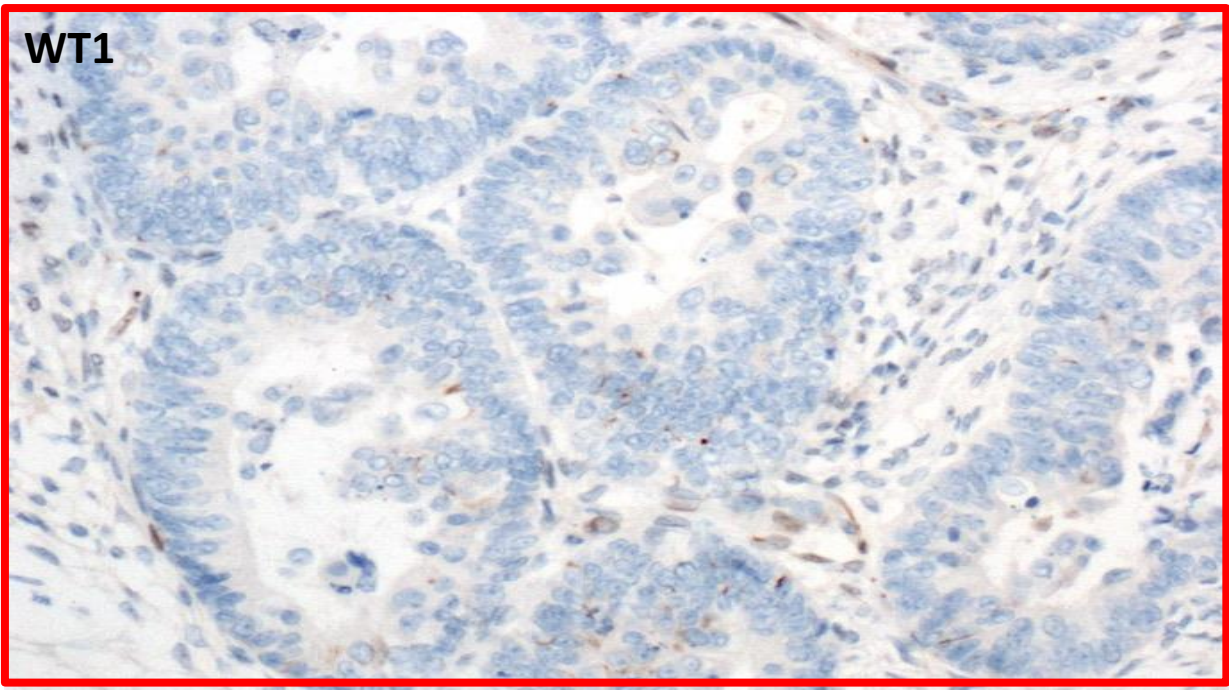
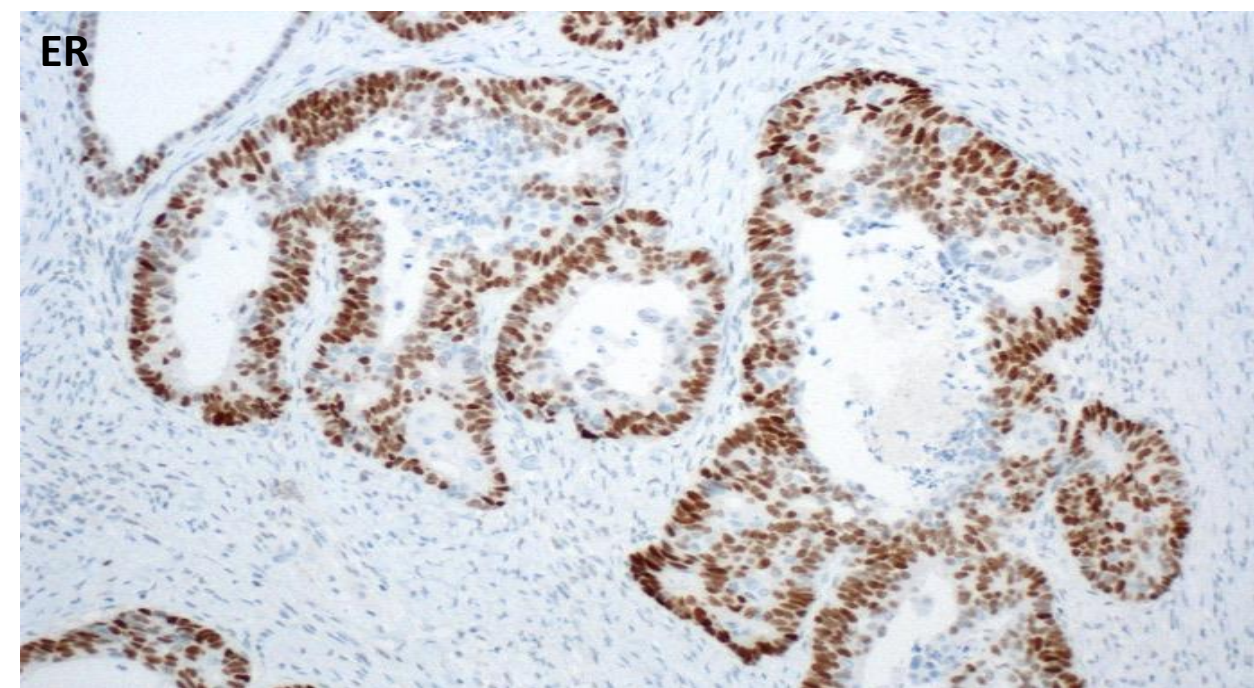
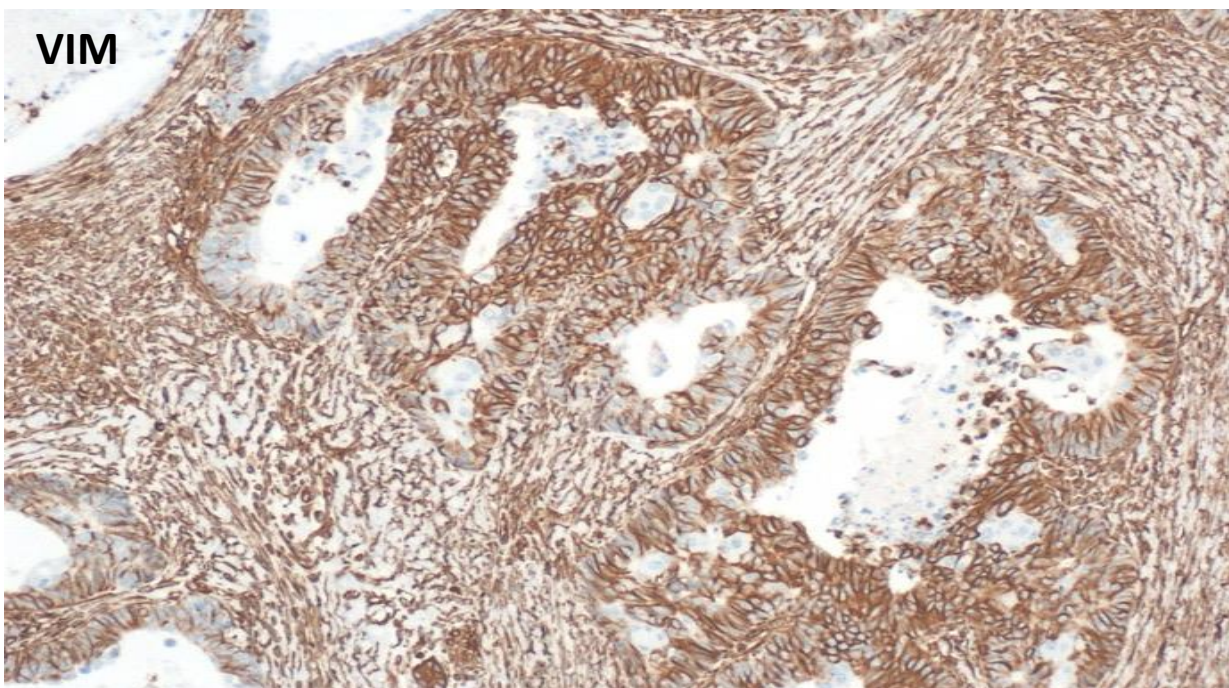
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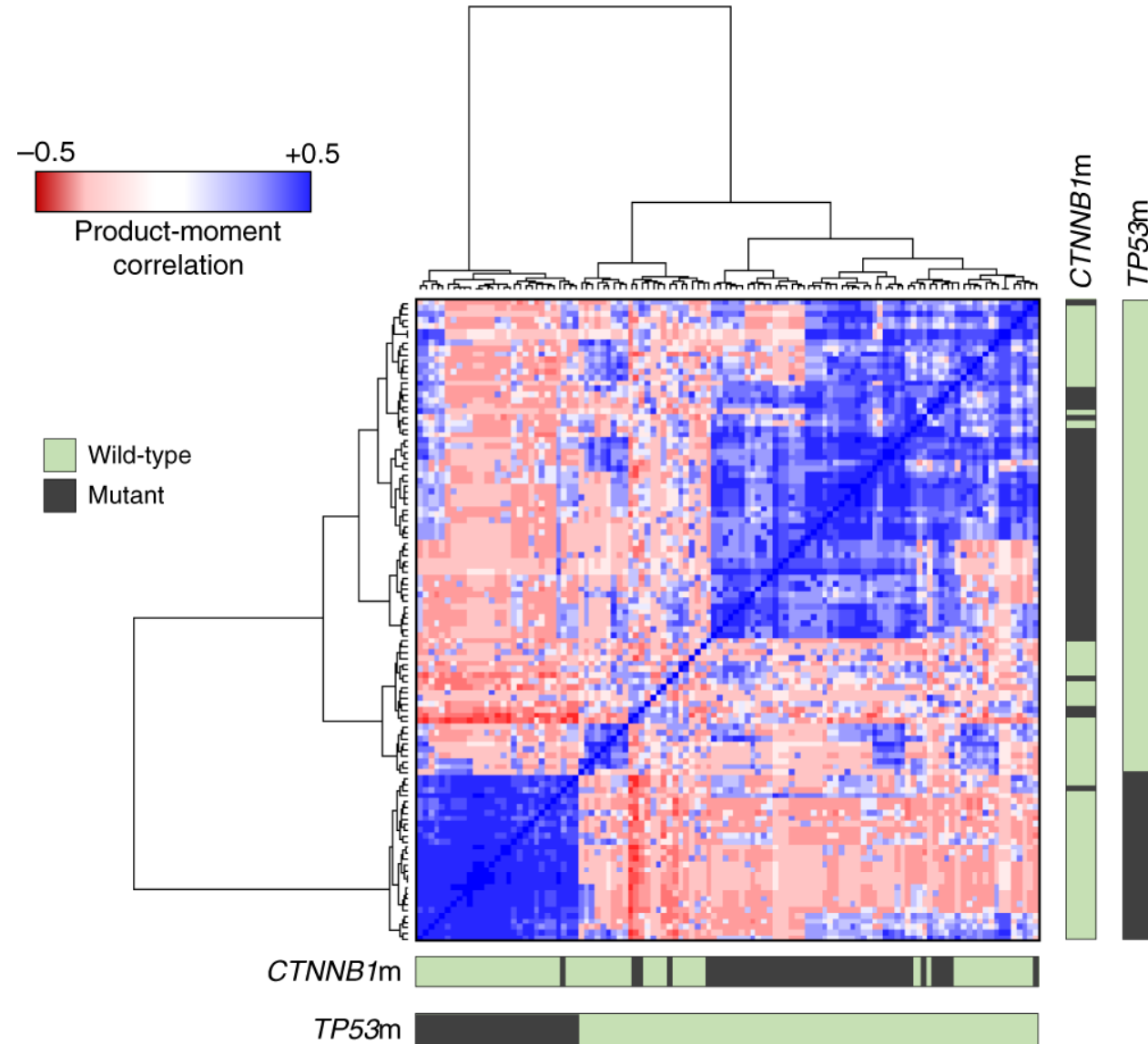
Endometrioid Carcinoma

- Associated with endometriosis and endometrioid hyperplasia
- Also associated with Lynch syndrome
- Borderline endometrioid tumours
 - Borderline adenofibroma
 - Atypical hyperplasia in endometriosis
- Synchronous endometrial endometrioid carcinoma may be present





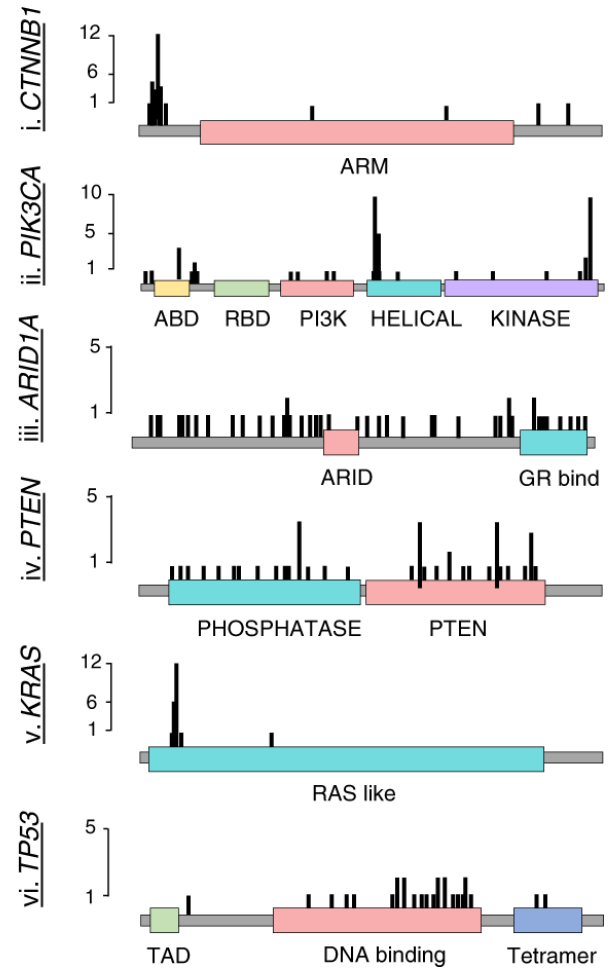
Unsupervised clustering of endometrioid ovarian carcinomas by patterns of mutation



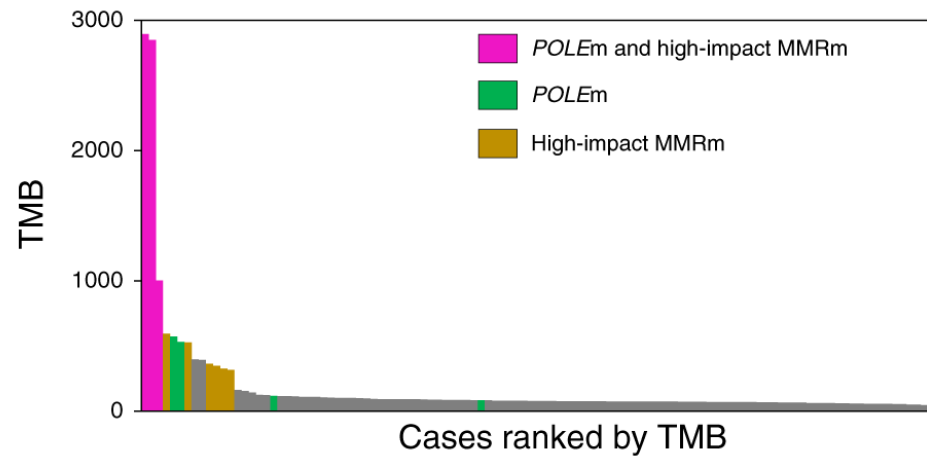
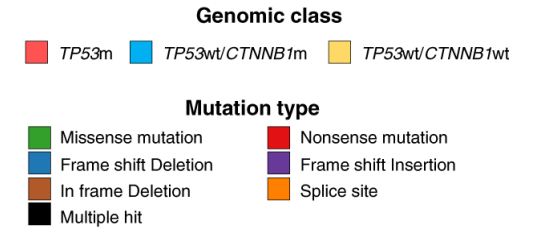
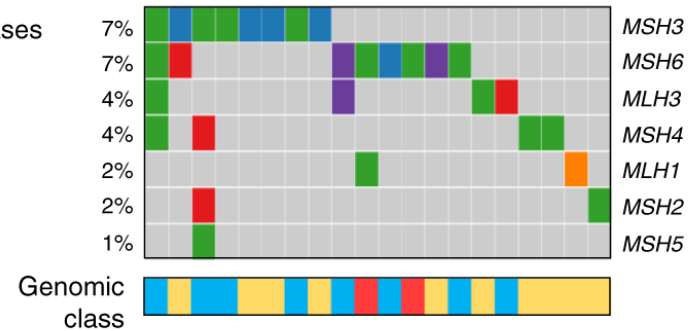
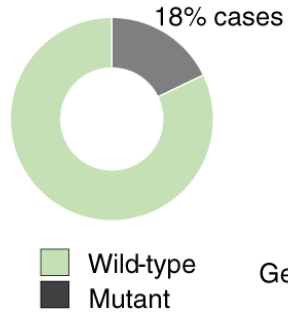
Genomic characterisation of endometrioid ovarian carcinomas



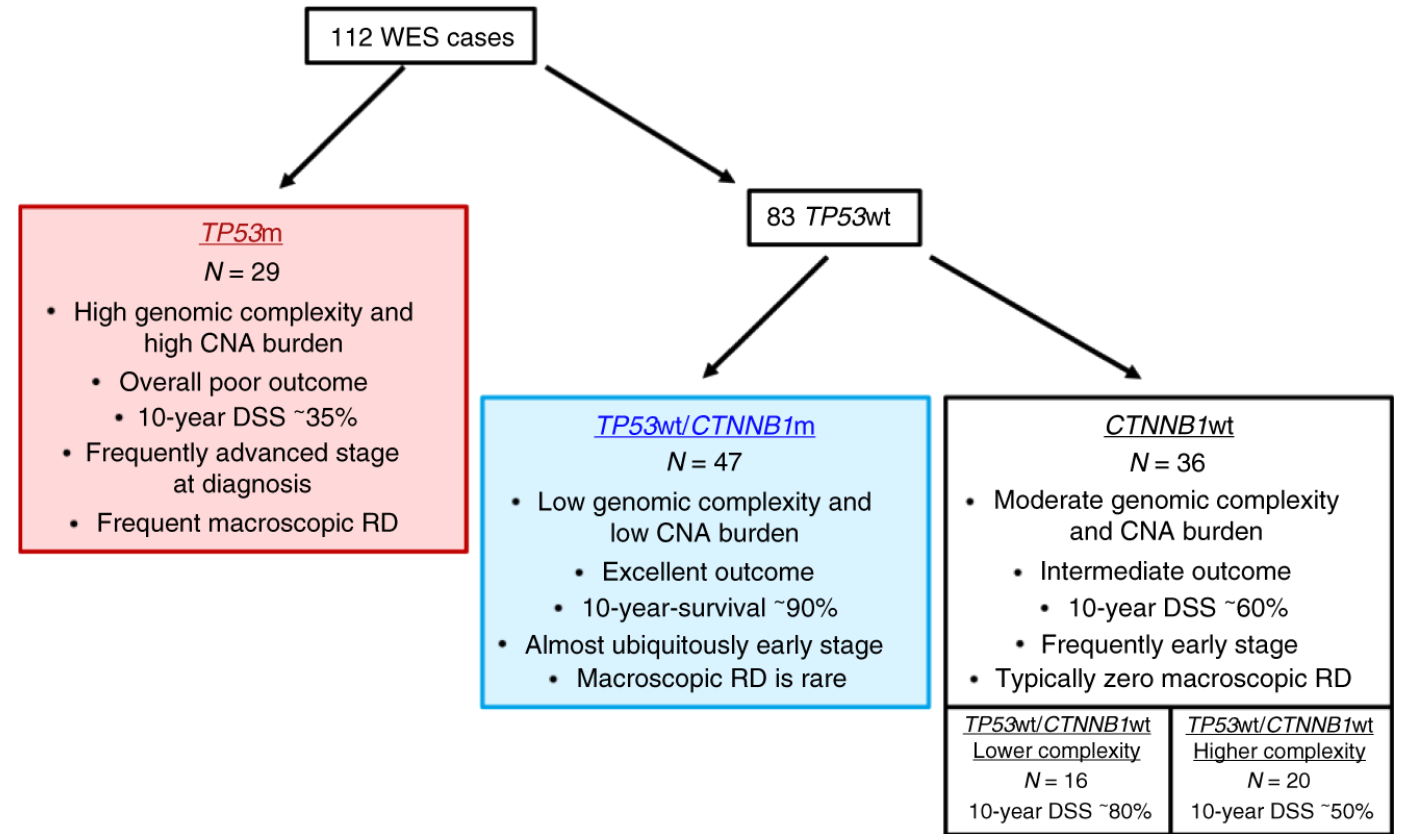
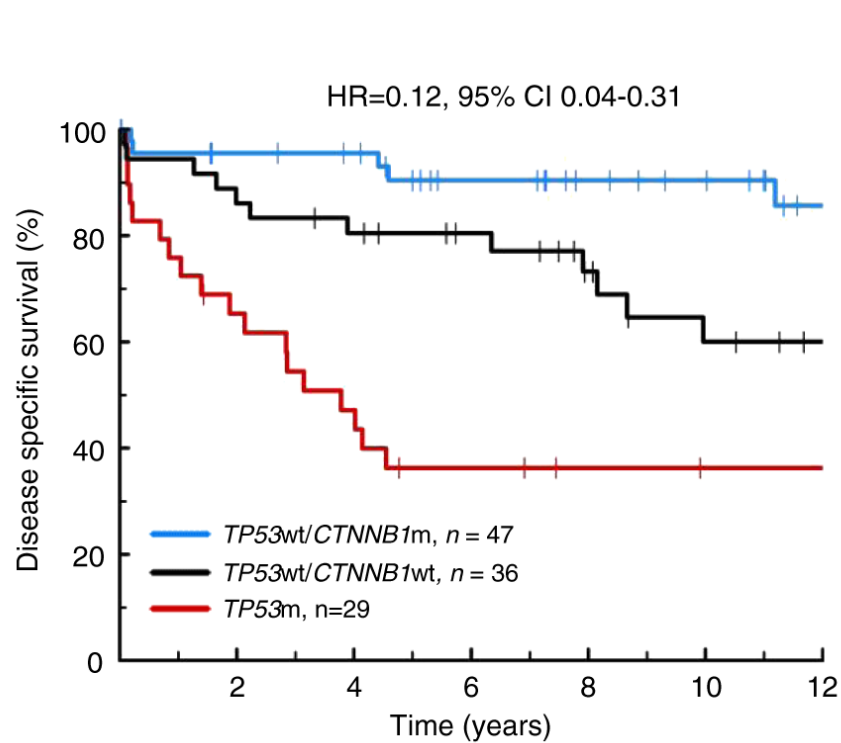
Genomic characterisation of endometrioid ovarian carcinomas



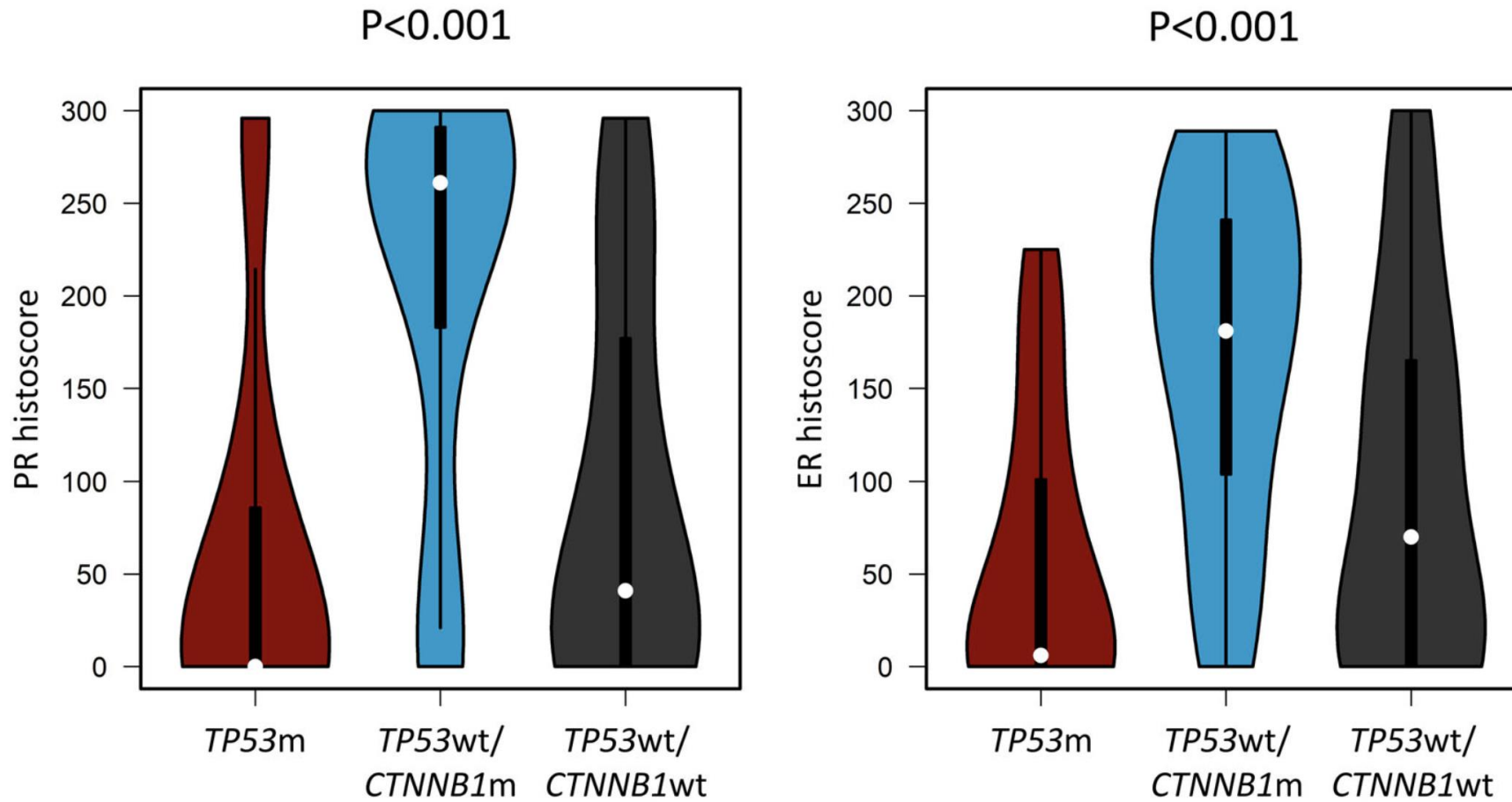
MMR mutations



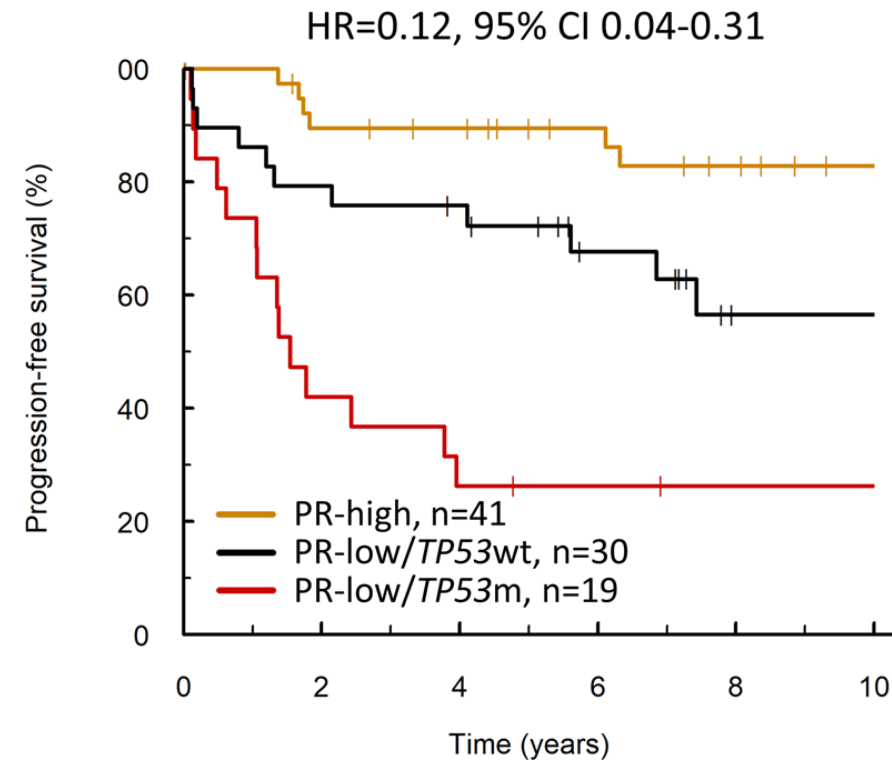
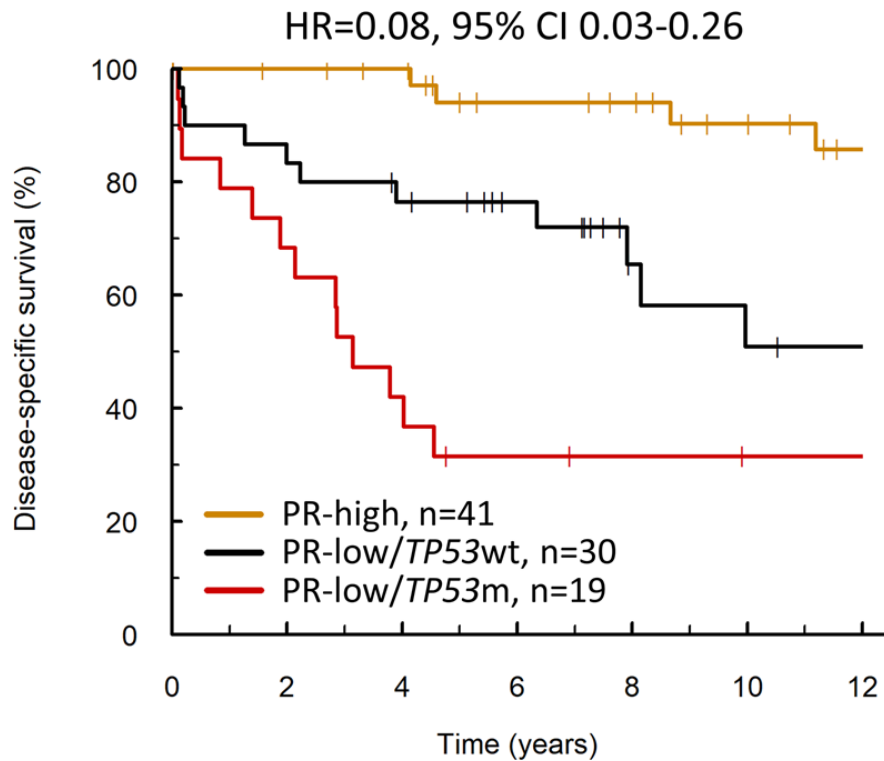
Genomic subtypes of endometrioid ovarian carcinoma demonstrate distinct clinical behaviour



Hormone receptor expression across genomic subtypes of endometrioid ovarian carcinoma



Clinical outcome of endometrioid ovarian carcinoma cases defined by combined PR-based subtyping and *TP53* mutation status



Synchronous Ovarian and Endometrial Carcinomas

- If either is non-endometrioid, consider as separate tumours
- If both endometrioid:
 - Most are clonally related
 - Have good prognosis and should be managed as two independent primary tumours if:
 - No more than superficial myometrial invasion
 - No lymphovascular invasion
 - Low grade endometrioid morphology
 - Absence of metastases elsewhere
 - Both tumours limited to the organ (stage 'IA')

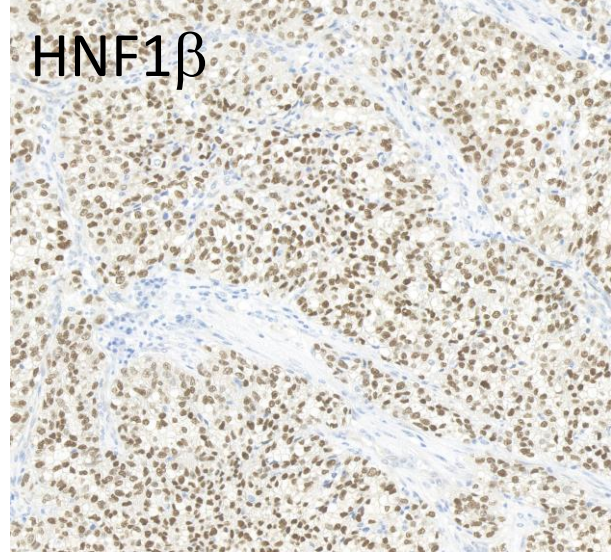
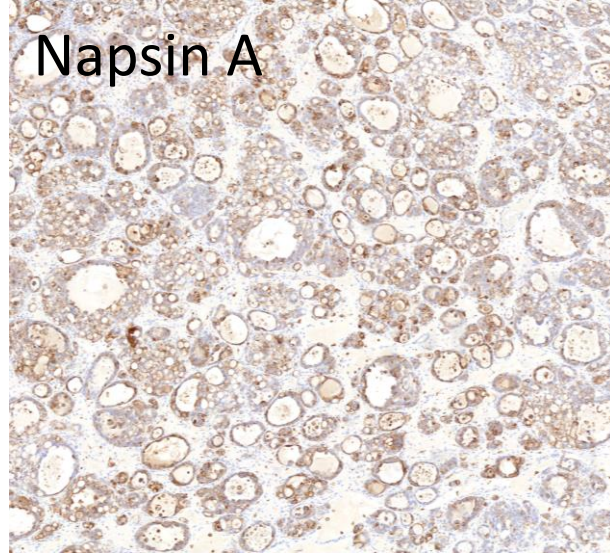
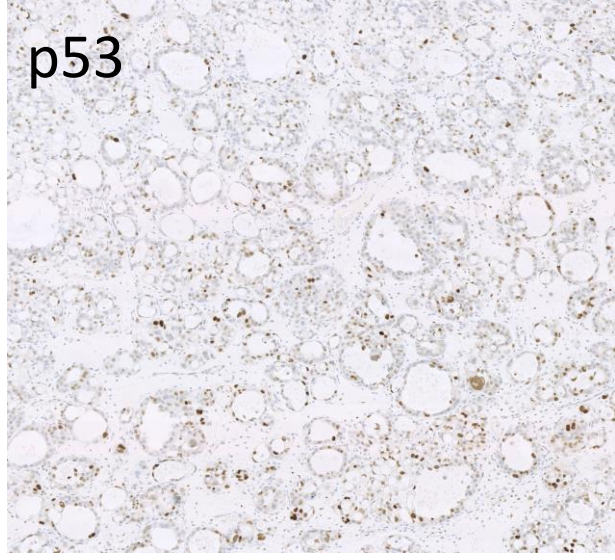
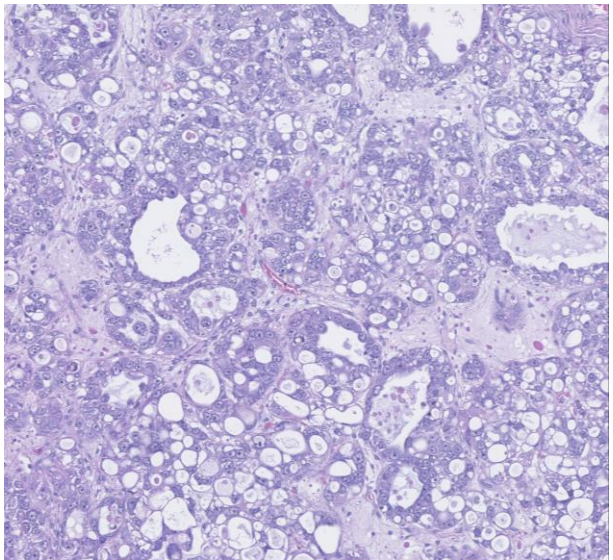
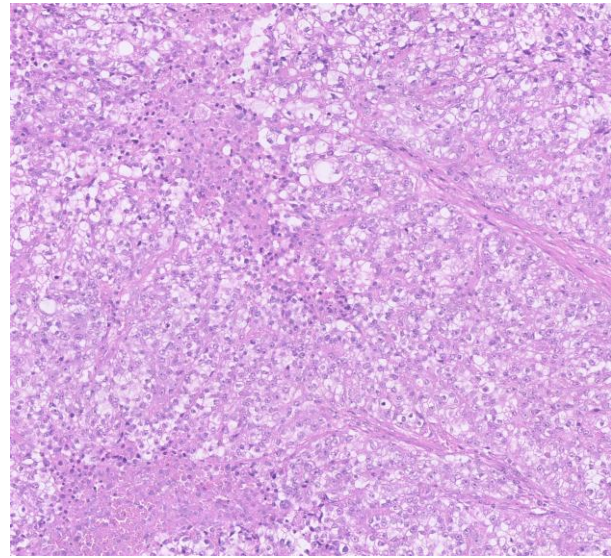
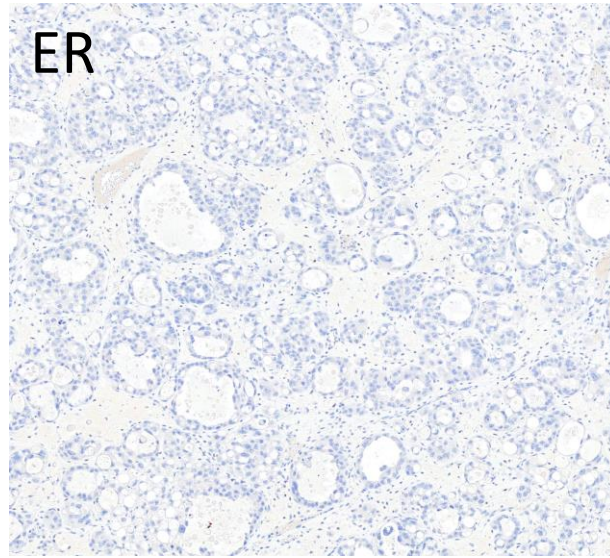
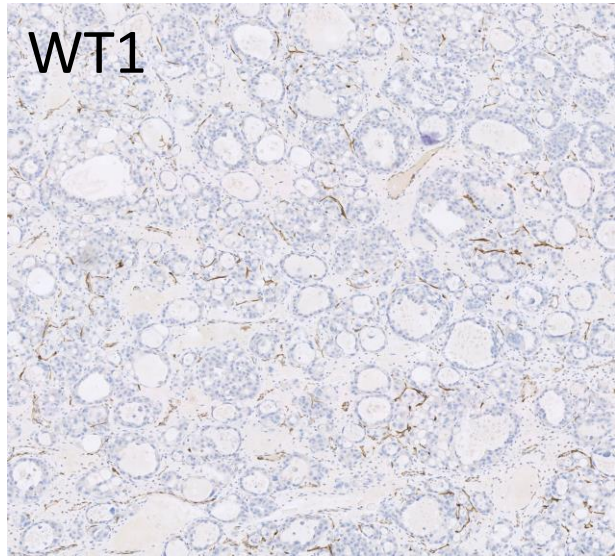
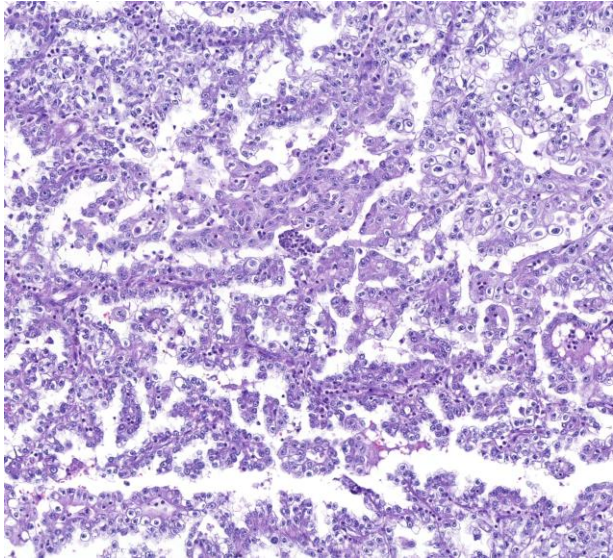
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Clear Cell Carcinoma

- Differential diagnosis
 - High-grade serous carcinoma with clear cells
 - Low grade serous carcinoma (when papillary)
 - Endometrioid carcinoma with secretory change or squamous differentiation
- Straightforward when classical
- Diagnosis supported by immunoprofile
 - WT1 negative, p53 wild type (around 5% aberrant), ER/PR negative
 - Napsin A, HNF1 β positive

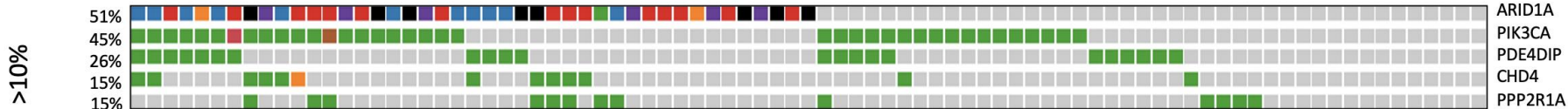
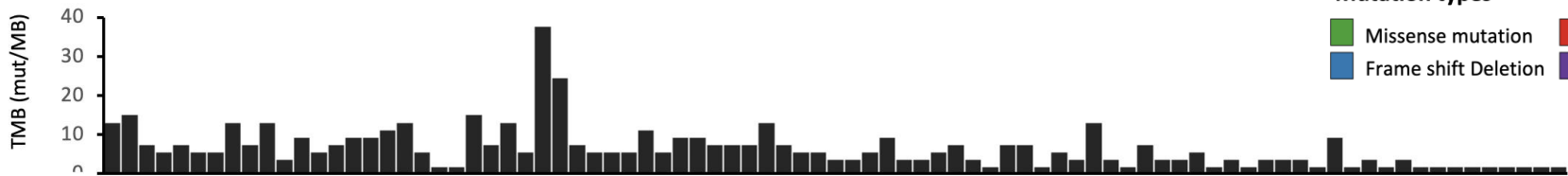
Clear Cell Carcinoma



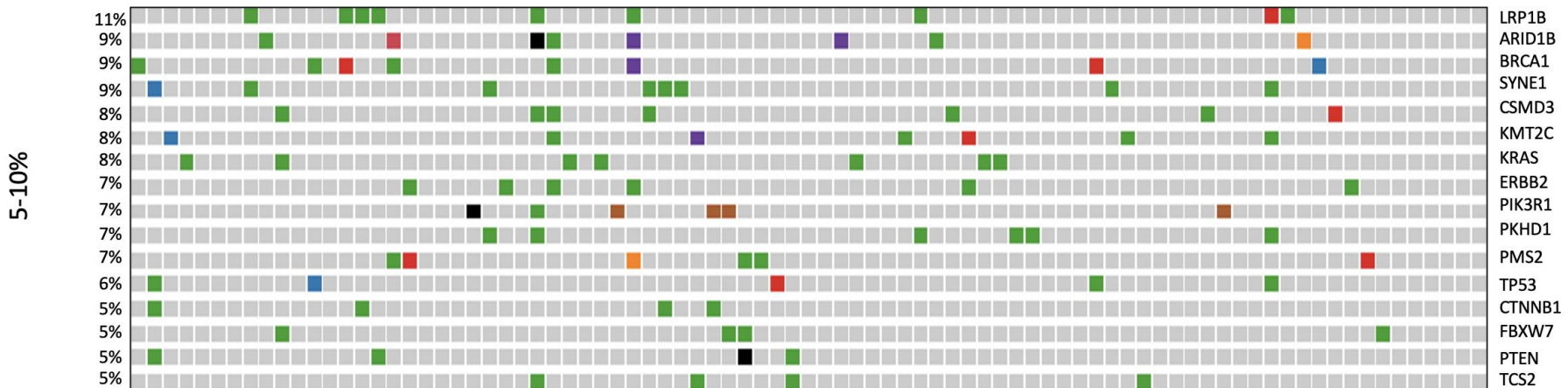
Mutational Profile of Clear Cell Carcinoma

Mutation types

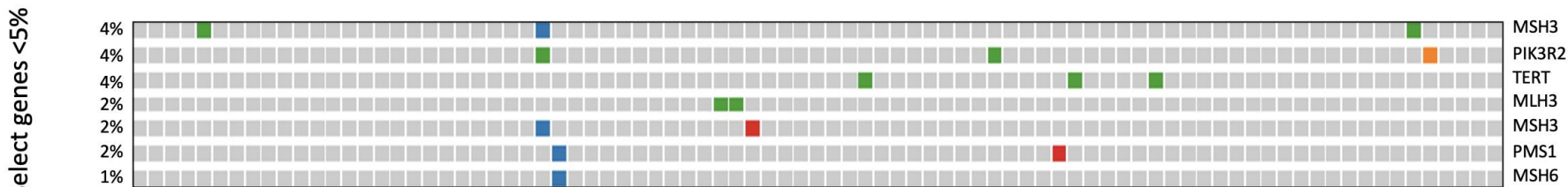
- Missense mutation
- Nonsense mutation
- In frame Deletion
- Multiple hit
- Frame shift Deletion
- Frame shift Insertion
- Splice site



ARID1A, PIK3CA common



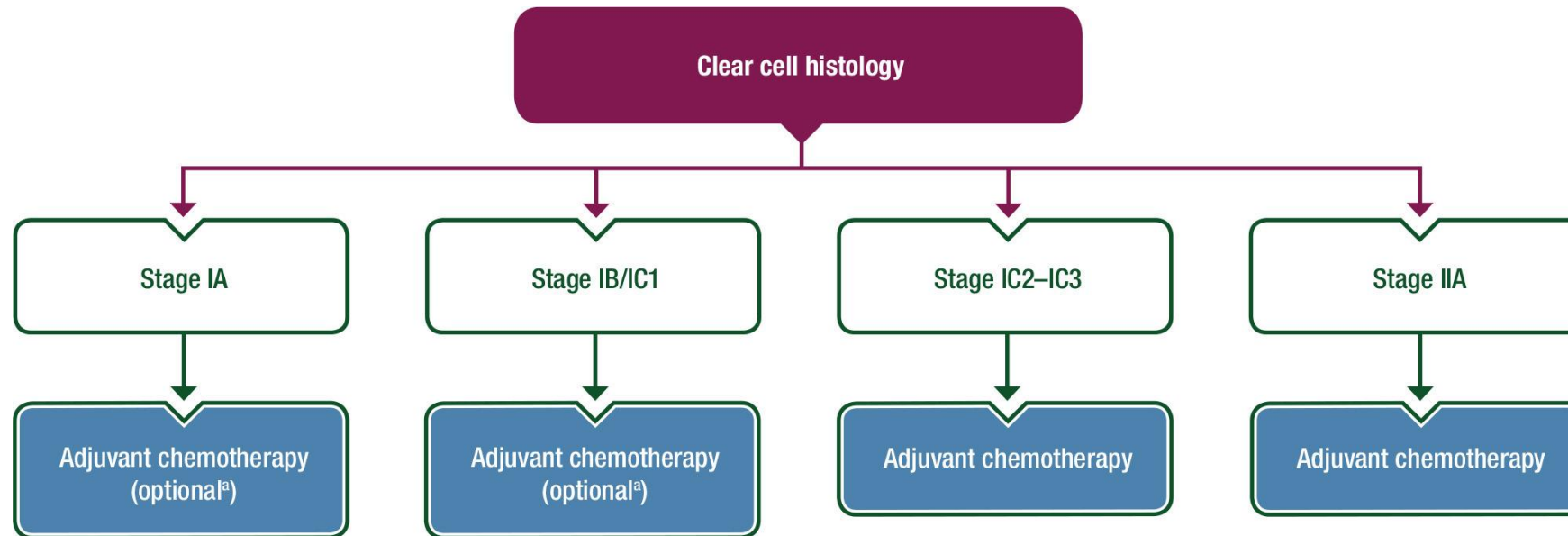
TP53, CTNNB1 uncommon



Preliminary, unpublished

Clear Cell Carcinoma

- Low stage disease has a good outcome
- High stage disease has a poor outcome



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Mucinous carcinoma

- Seromucinous carcinoma
 - Associated with endometriosis
 - Deleted from WHO 2020 as now considered a variant of endometrioid carcinoma
 - Supported by immunoprofile:
 - PAX8, ER/PR, CA125 positive; p53 wild type; WT1 negative
- Mucinous carcinoma of intestinal type
 - Immunoprofile reflects intestinal differentiation
 - PAX8, ER/PR, WT1 negative, cytokeratin profile variable
 - HER2 testing may be of value

Morphologic Reproducibility, Genotyping, and Immunohistochemical Profiling Do Not Support a Category of Seromucinous Carcinoma of the Ovary

Peter F. Rambau, MD,† John B. McIntyre, PhD,‡ Jennifer Taylor, MD,§ Sandra Lee, MD,*
Travis Ogilvie, MD,* Anna Sienko, MD,* Don Morris, MD,‡|| Máire A. Duggan, MD,*
W. Glenn McCluggage, MD,§ and Martin Köbel, MD**

Am J Surg Pathol 2017; 41: 685-695

Endometriosis-related pathology: a discussion of selected uncommon benign, premalignant and malignant lesions

W Glenn McCluggage 
Department of Pathology, Belfast Health and Social Care Trust, Belfast, UK

Histopathology 2020; 76: 76-92

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Ovarian Epithelial Tumours

← Carcinosarcoma / undifferentiated carcinoma →

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	High-Grade Serous	Low-Grade Serous	Endometrioid	Seromucinous	Clear cell	Mucinous	Brenner
Borderline /AP		KRAS BRAF	CTNNB1 TP53 PIK3CA ARID1A PTEN Lynch		ARID1A PIK3CA TP53 CTNNB1 PTEN Lynch	KRAS	
Grade 1							
Grade 2	TP53 BRCA Cyclin E		Endometrioid	Endometrioid	ARID1A PIK3CA TP53 CTNNB1 PTEN Lynch		
Grade 3	NF1 RB1 RNA						

Mixed Tumours

- Improved recognition of types has virtually abolished mixed epithelial tumours
 - 15 of 871 cases reviewed (1.7%)
- 22 cases thought to be mixed were investigated further by molecular testing
- Only 13 true mixed tumours when molecular data incorporated

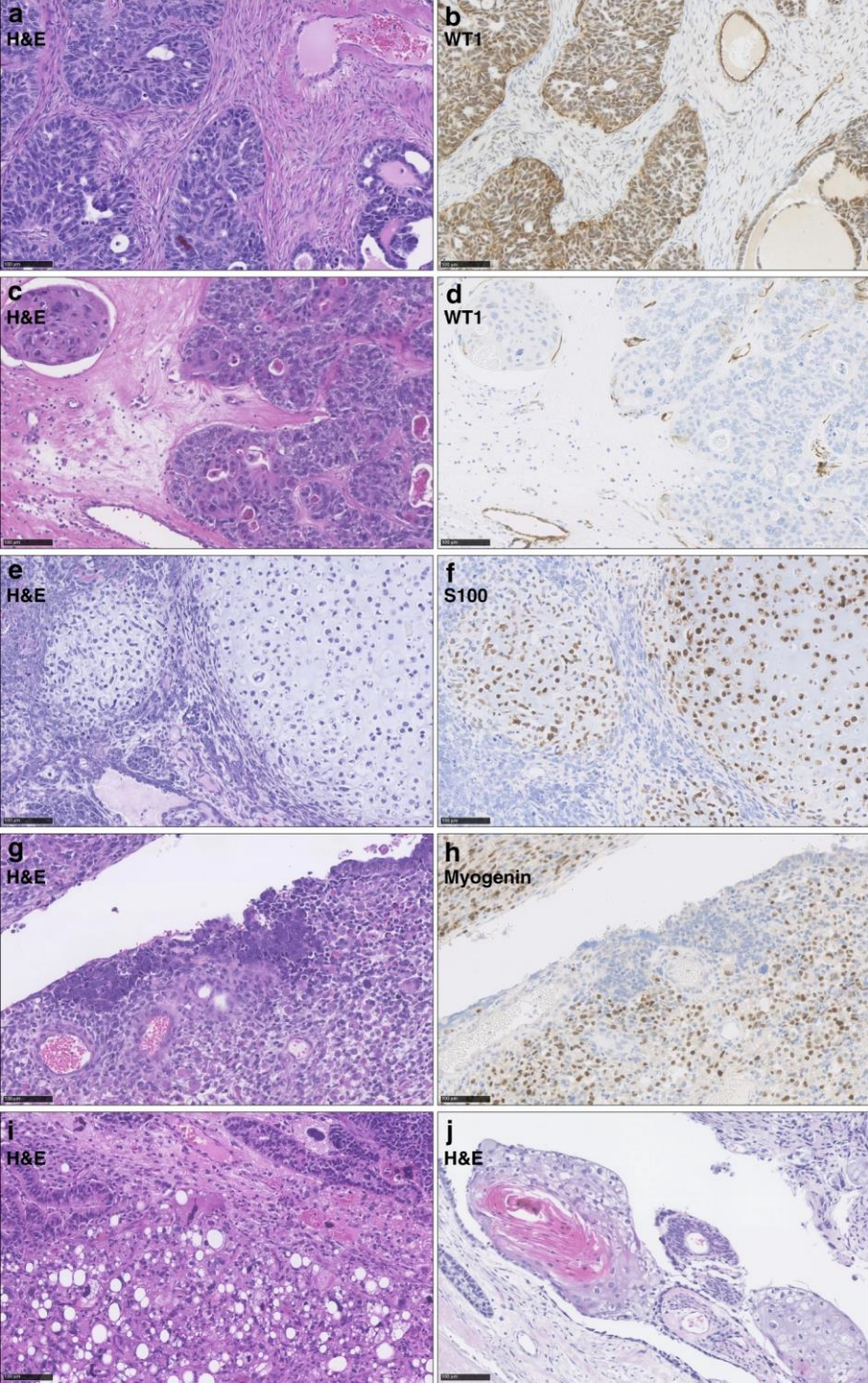
Mackenzie et al Am J Surg Pathol 2015; 39: 1548-1557

Other Tumours

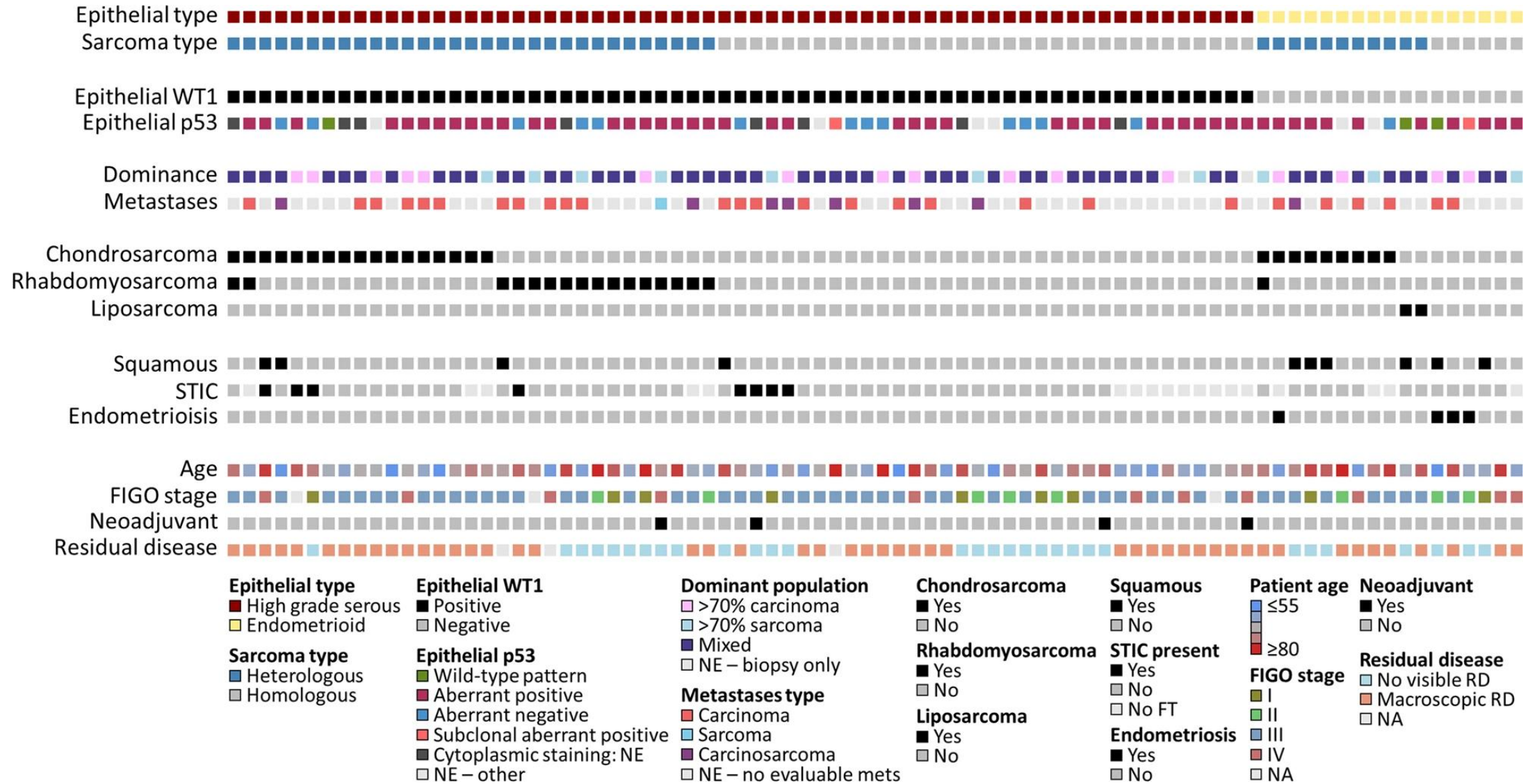
- Carcinosarcoma
- Small cell carcinoma, hypercalcaemic type
- Dedifferentiated / undifferentiated carcinoma
- Mesonephric-like carcinoma

Carcinosarcoma

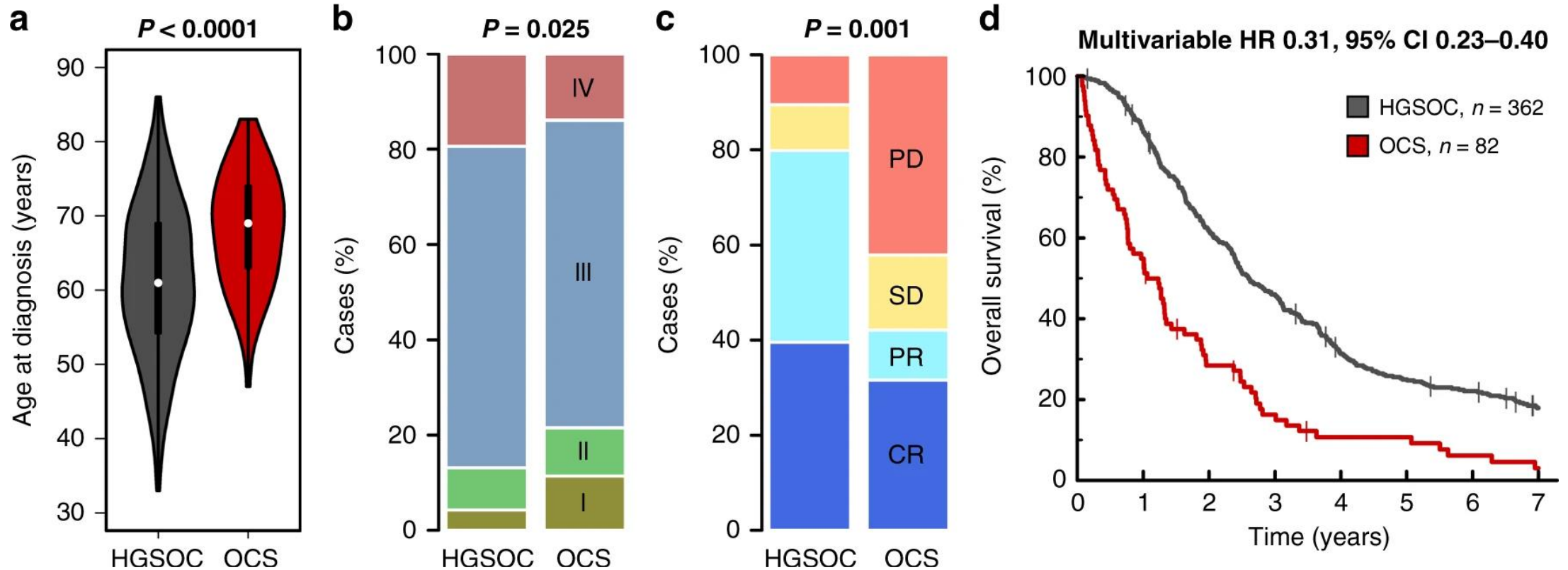
- Not just high-grade serous carcinoma with a sarcomatous component
- Associated with poorer outcome than high-grade serous carcinoma, independent of epithelial type
- Can molecular features help to predict more aggressive behaviour in endometrioid and high-grade serous carcinomas?



Carcinosarcoma



Carcinosarcoma vs High-Grade Serous Carcinoma



Small cell carcinoma, hypercalcaemic type

- Characterised by *SMARCA4* mutation (almost all cases) leading to loss of expression of BRG1
- Immunohistochemistry for BRG1 and INI1 (*SMARCB1*) aids diagnosis
- Germline mutation is present in a significant proportion of patients
- Loss of BRM (*SMARCA2*) may also be useful
- Specificity not as high as initially reported

Journal of Pathology

J Pathol 2016; 238: 389–400

Published online 21 December 2015 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/path.4633

ORIGINAL PAPER

Dual loss of the SWI/SNF complex ATPases SMARCA4/BRG1 and SMARCA2/BRM is highly sensitive and specific for small cell carcinoma of the ovary, hypercalcaemic type

Anthony N Karnezis,^{1†} Yemin Wang,^{1†} Pilar Ramos,^{2†} William PD Hendricks,² Esther Oliva,³ Emanuela D'Angelo,⁴ Jaime Prat,⁴ Marisa R Nucci,⁵ Torsten O Nielsen,¹ Christine Chow,⁶ Samuel Leung,⁶ Friedrich Kommos,⁷ Stefan Kommos,⁸ Annacarina Silva,⁹ Brigitte M Ronnett,¹⁰ Joseph T Rabban,¹¹ David D Bowtell,¹² Bernard E Weissman,¹³ Jeffrey M Trent,² C Blake Gilks^{1*} and David G Huntsman^{1,6,14*}

Histopathology

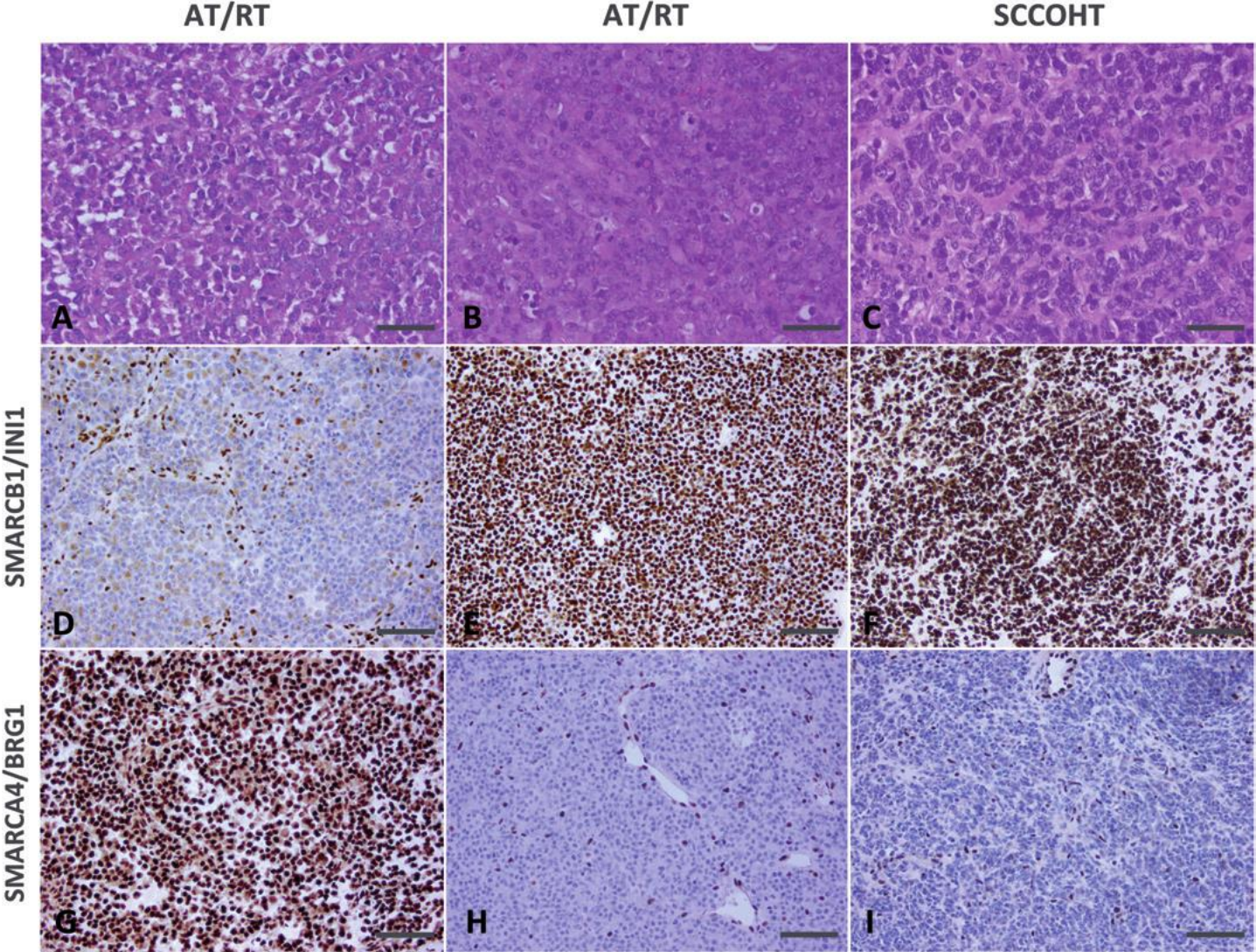


Histopathology 2017, 70, 359–366. DOI: 10.1111/his.13091

Loss of expression of SMARCA4 (BRG1), SMARCA2 (BRM) and SMARCB1 (INI1) in undifferentiated carcinoma of the endometrium is not uncommon and is not always associated with rhabdoid morphology

Preetha Ramalingam,¹ Sabrina Croce² & W Glenn McCluggage³

BRG1 Loss in Small Cell Carcinoma, Hypercalcaemic Type



Dedifferentiated / undifferentiated Carcinoma

MODERN PATHOLOGY (2016) 29, 1586–1593

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Concurrent ARID1A and ARID1B inactivation in endometrial and ovarian dedifferentiated carcinomas

Mackenzie Coatham¹, Xiaodong Li², Anthony N Karnezis³, Lien N Hoang^{3,4}, Basile Tessier-Cloutier³, Bo Meng², Robert A Soslow⁴, C Blake Gilks³, David G Huntsman³, Colin J R Stewart⁵, Lynne M Postovit¹, Martin Köbel^{6,7} and Cheng-Han Lee^{2,7}

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Review article

SWI/SNF-deficient malignancies of the female genital tract

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Histopathology



Histopathology 2021, 79, 160–167. DOI: 10.1111/his.14333

Loss of ARID1B and SMARCB1 expression are specific for the diagnosis of dedifferentiated/undifferentiated carcinoma in tumours of the upper gynaecological tract and cervix

Eun-Young Kang,¹ Basile Tessier-Cloutier,² Máire A Duggan,¹ Colin J R Stewart,³ Cheng-Han Lee^{2,4} & Martin Köbel¹

The Journal of Pathology: Clinical Research

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ORIGINAL ARTICLE

SWI/SNF-deficiency defines highly aggressive undifferentiated endometrial carcinoma

Basile Tessier-Cloutier¹, Mackenzie Coatham², Mark Carey³, Gregg S Nelson⁴, Sarah Hamilton⁵, Amy Lum¹, Robert A Soslow⁶, Colin JR Stewart⁷, Lynne M Postovit², Martin Köbel^{8†} and Cheng-Han Lee^{9,10†*}

Mesonephric-like Adenocarcinoma

- Resemble cervical mesonephric carcinoma morphologically
- Likely Müllerian derivation as associated with endometriosis and other Müllerian tumours
- No squamous or mucinous differentiation, unlike endometrioid carcinoma
- Typically GATA3 and TTF1 positive
- ER/PR negative, WT1 negative, PAX8/CK7 positive
- *KRAS* hotspot mutations in almost all, *NRAS* mutations in the rest.
- Concurrent *PIK3CA* mutations in approximately 40% of *KRAS*-mutant MLA, but not in those with *NRAS* mutations

Future Directions

- Improved accuracy of primary diagnosis
- Improved stratification within tumour types for therapy
- Development of novel therapies based on improved understanding of tumour type and stratification

