# Endometriosis-associated Ovarian Tumours

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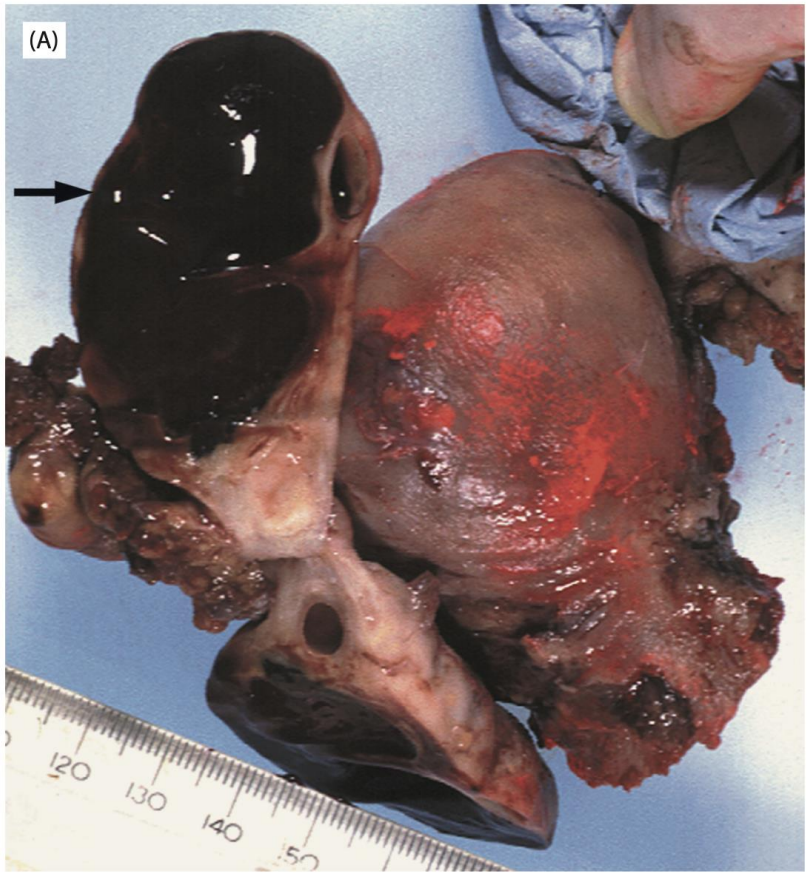
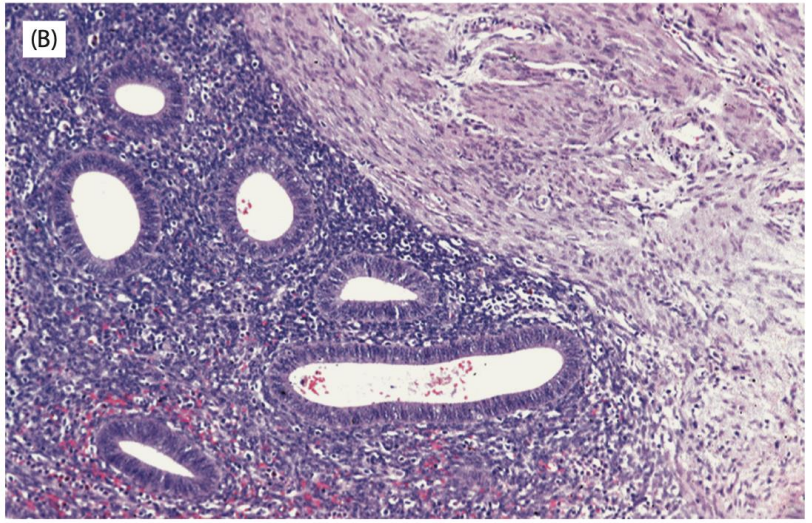
# Outline

- Endometriosis
- Endometriosis-associated tumours
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Mesonephric-like adenocarcinoma
- Future directions

# Endometriosis

- Endometrial tissue (glands and stroma) outside the uterine body
- Most common site is ovary
- Non-ovarian endometriosis may also give rise to endometriosis-associated tumours



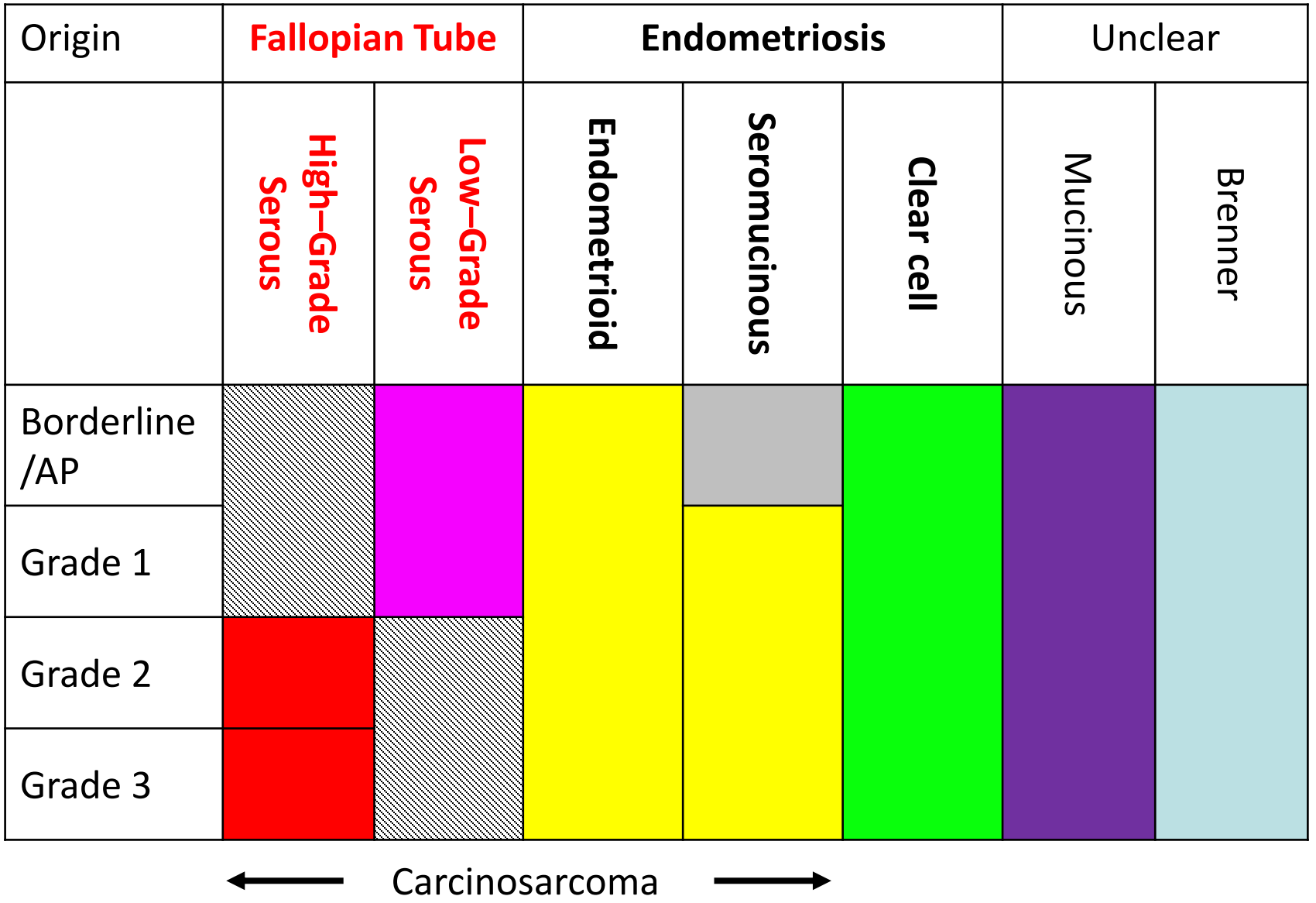




**Endometriosis-related pathology: a discussion of selected uncommon benign, premalignant and malignant lesions**

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

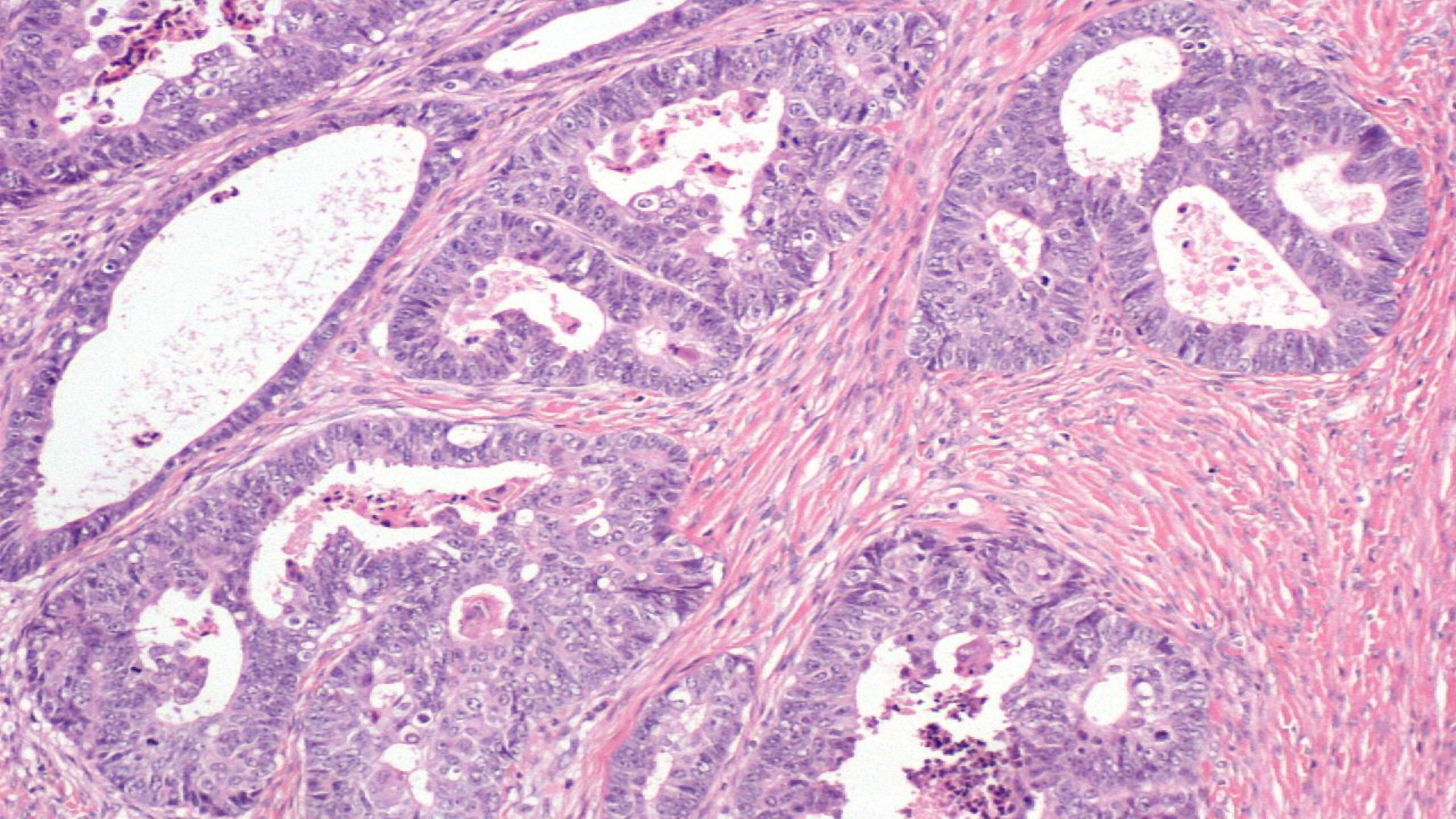
Histopathology 2020; 76: 76-92

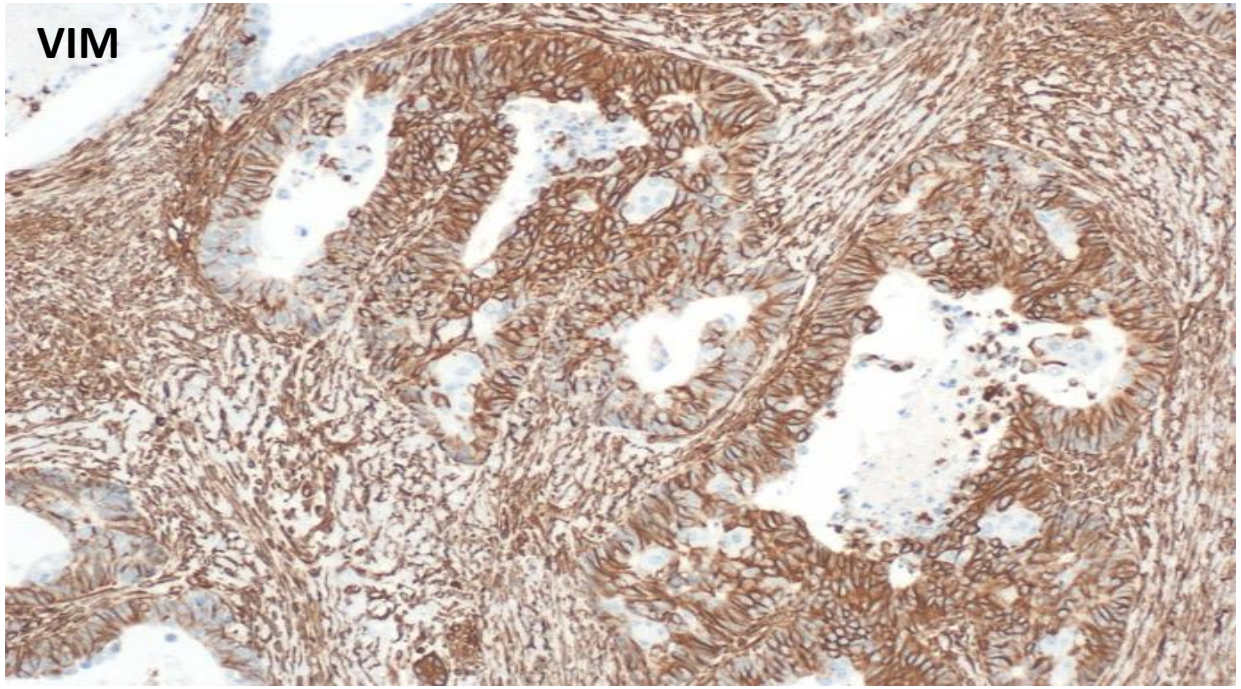
# Classification of Ovarian Epithelial Tumours



# Endometrioid Carcinoma

- Associated with:
  - Endometriosis and endometrioid hyperplasia
  - Lynch syndrome
  - Borderline endometrioid lesions
    - Borderline adenofibroma
    - Atypical hyperplasia/EIN in endometriosis
- Squamous and mucinous differentiation diagnostically helpful
- Synchronous endometrioid endometrial carcinoma may be present

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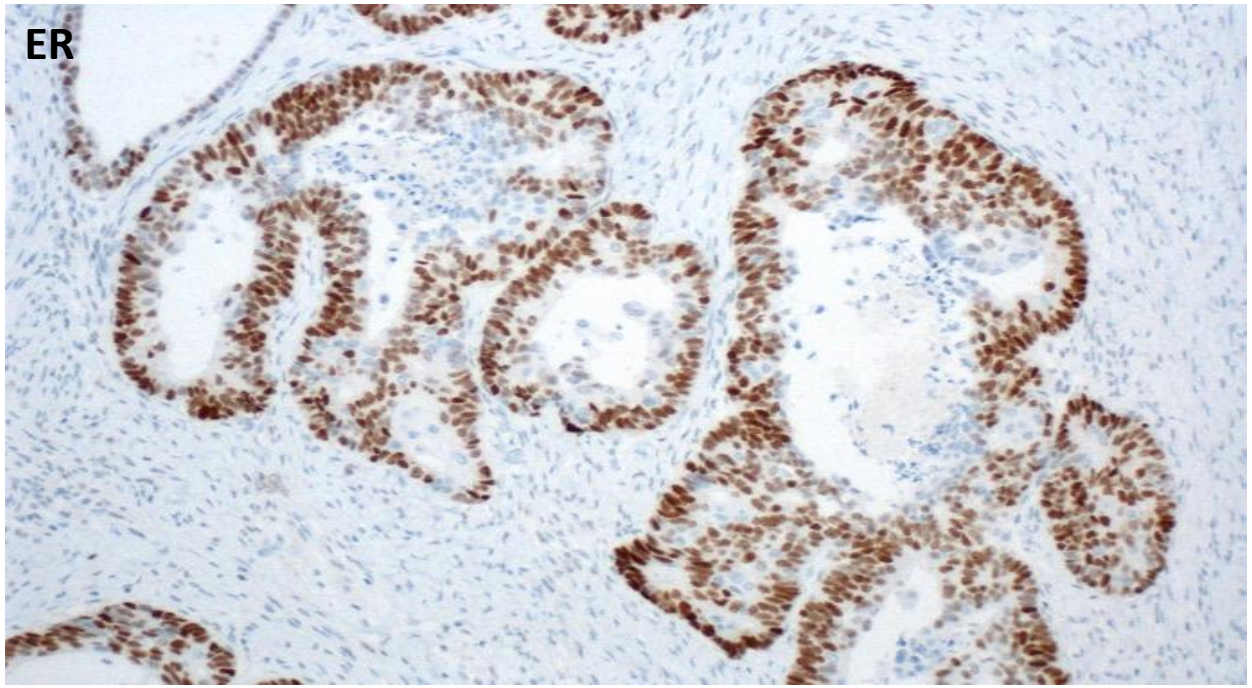
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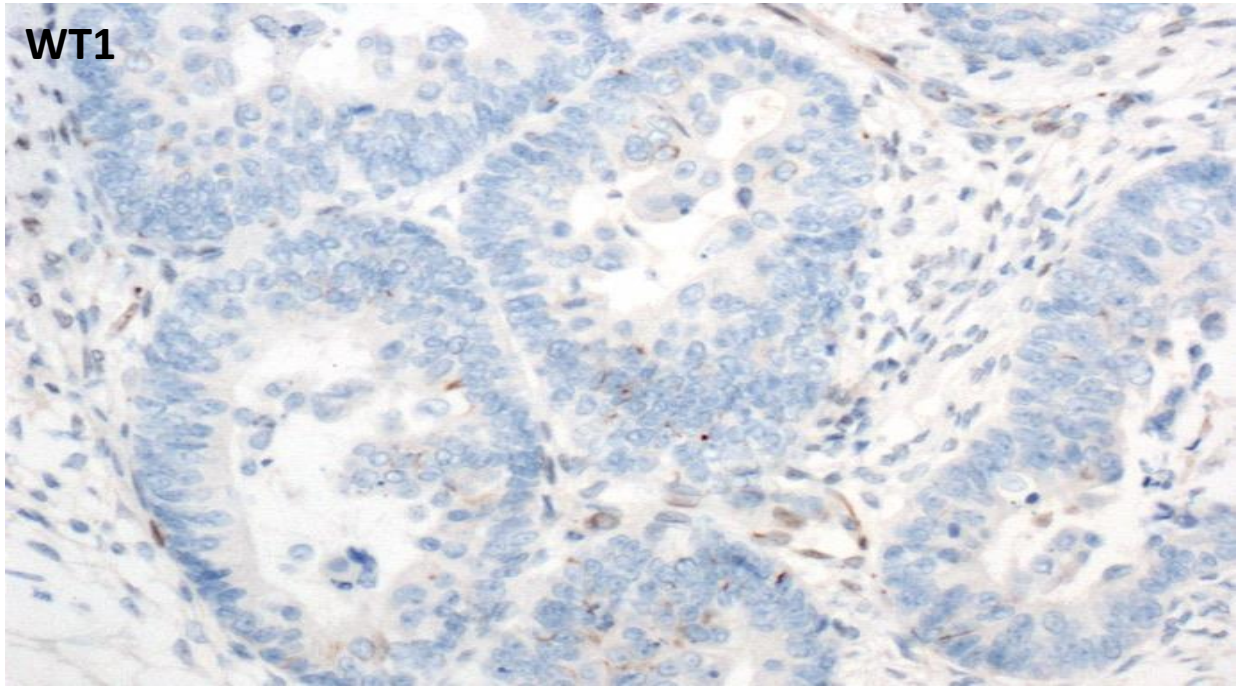
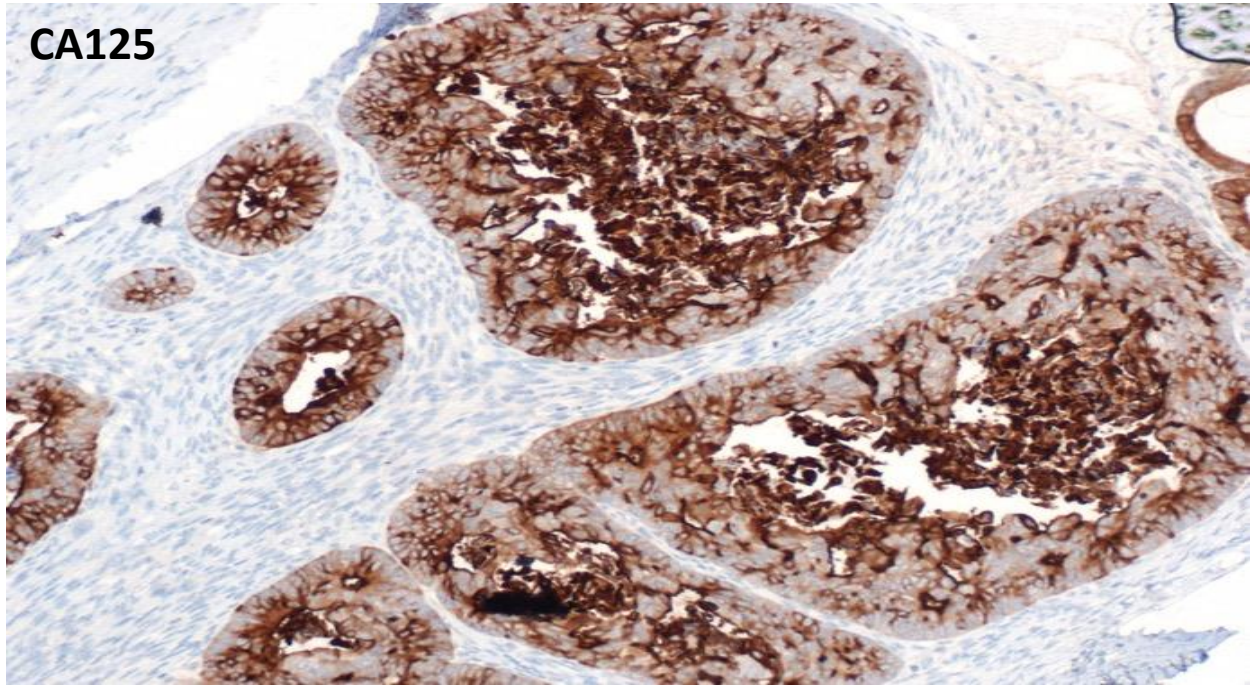
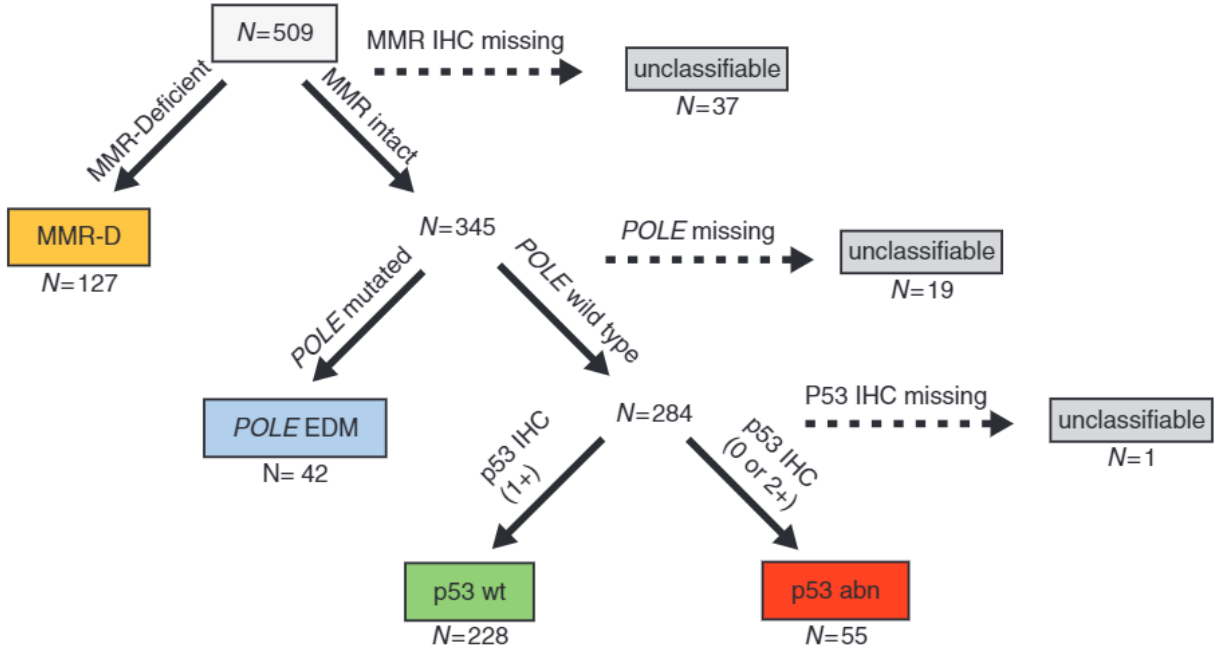
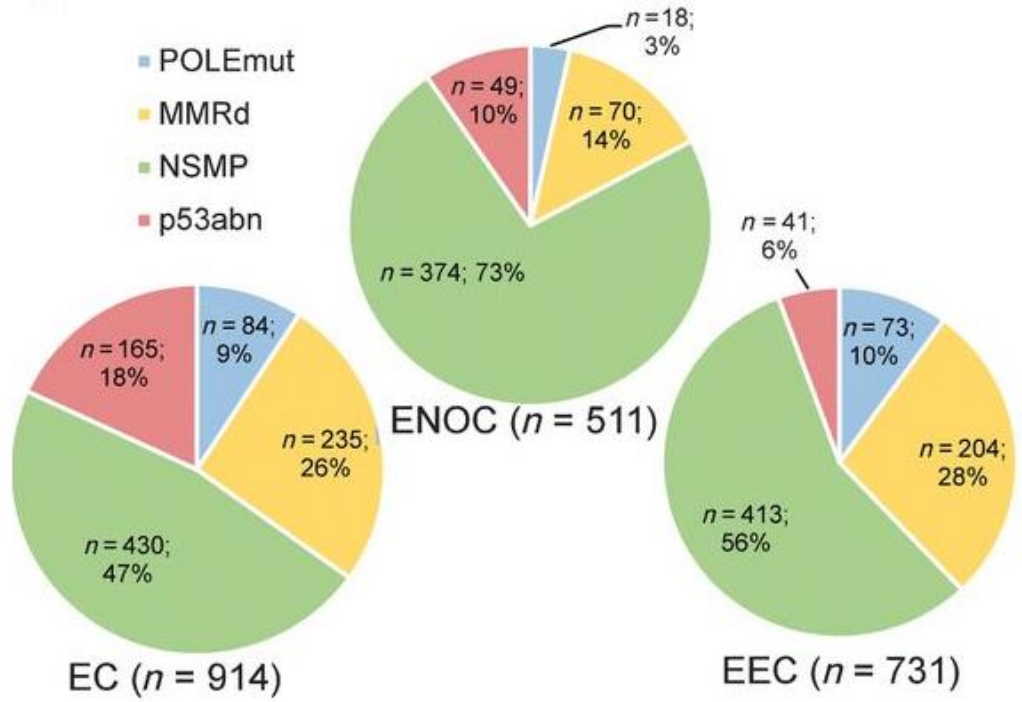

WT1


CA125

# Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)

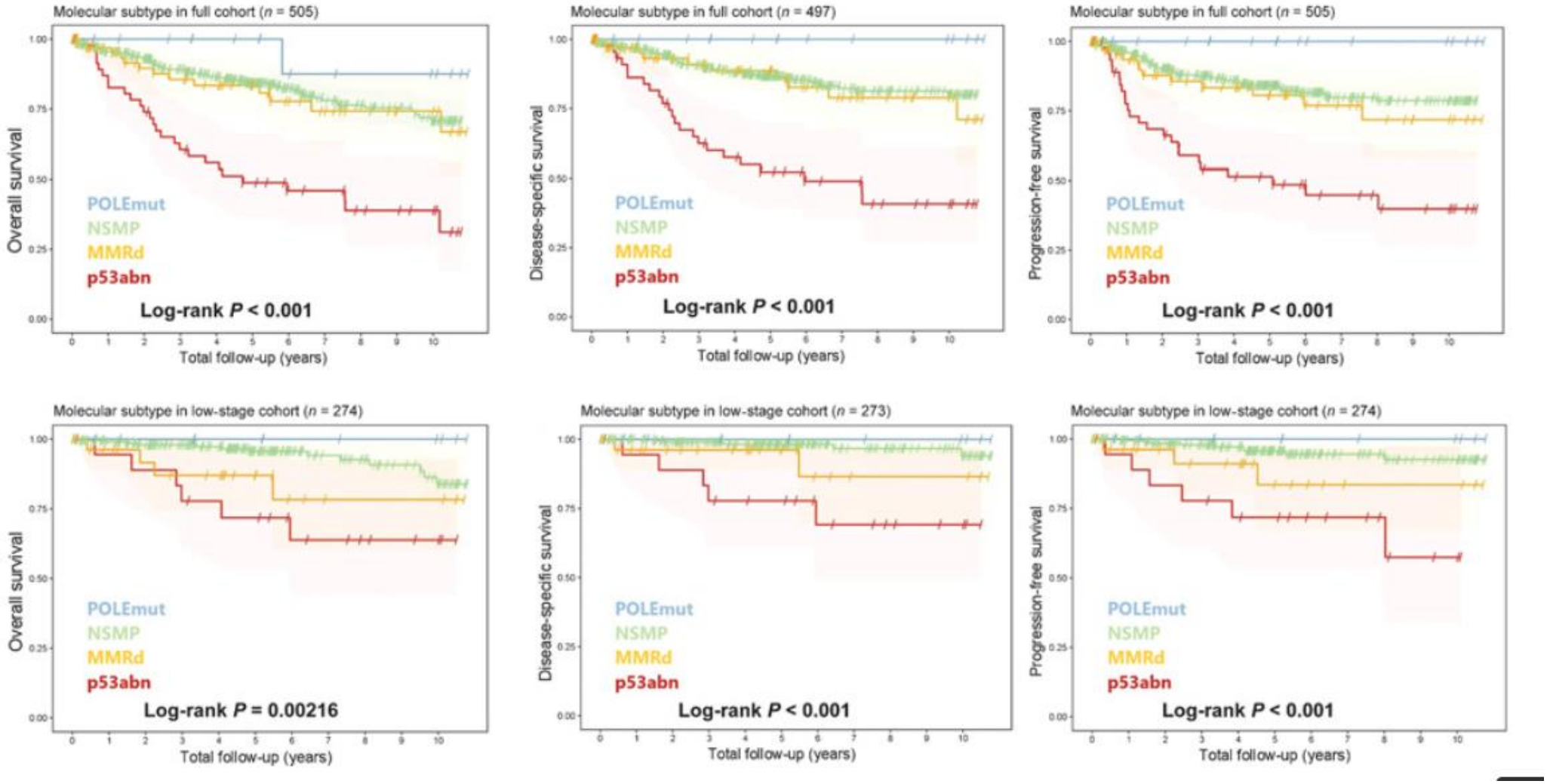



Kommoss S et al. Ann Oncol 2018; 29: 1180-1188

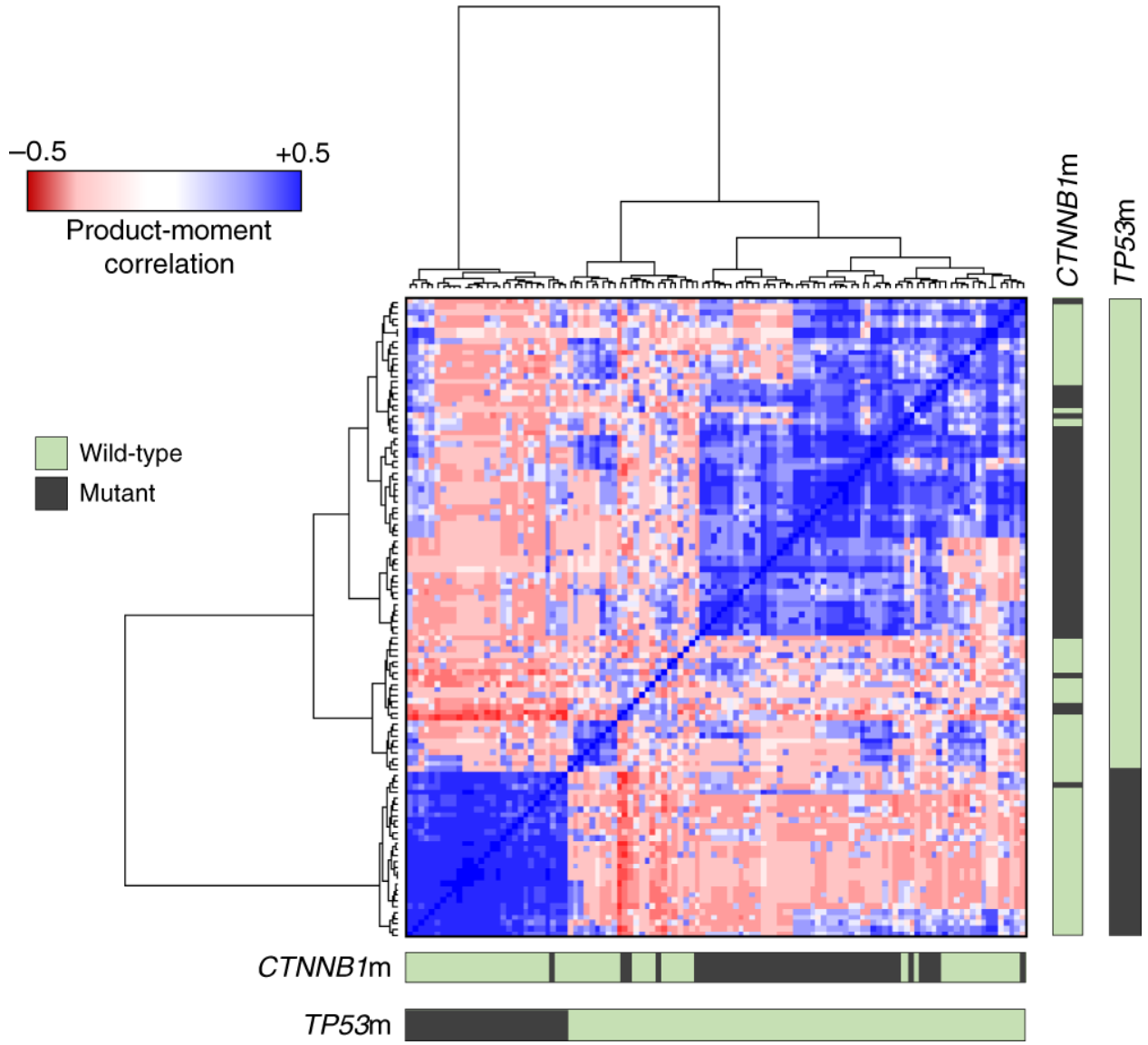
Kramer P, Talhouk A et al, Clin Cancer Res 2020; 26: 5400-5410

EC, endometrial carcinoma; ENOC, endometrioid ovarian carcinoma; EEC, endometrioid endometrial carcinoma



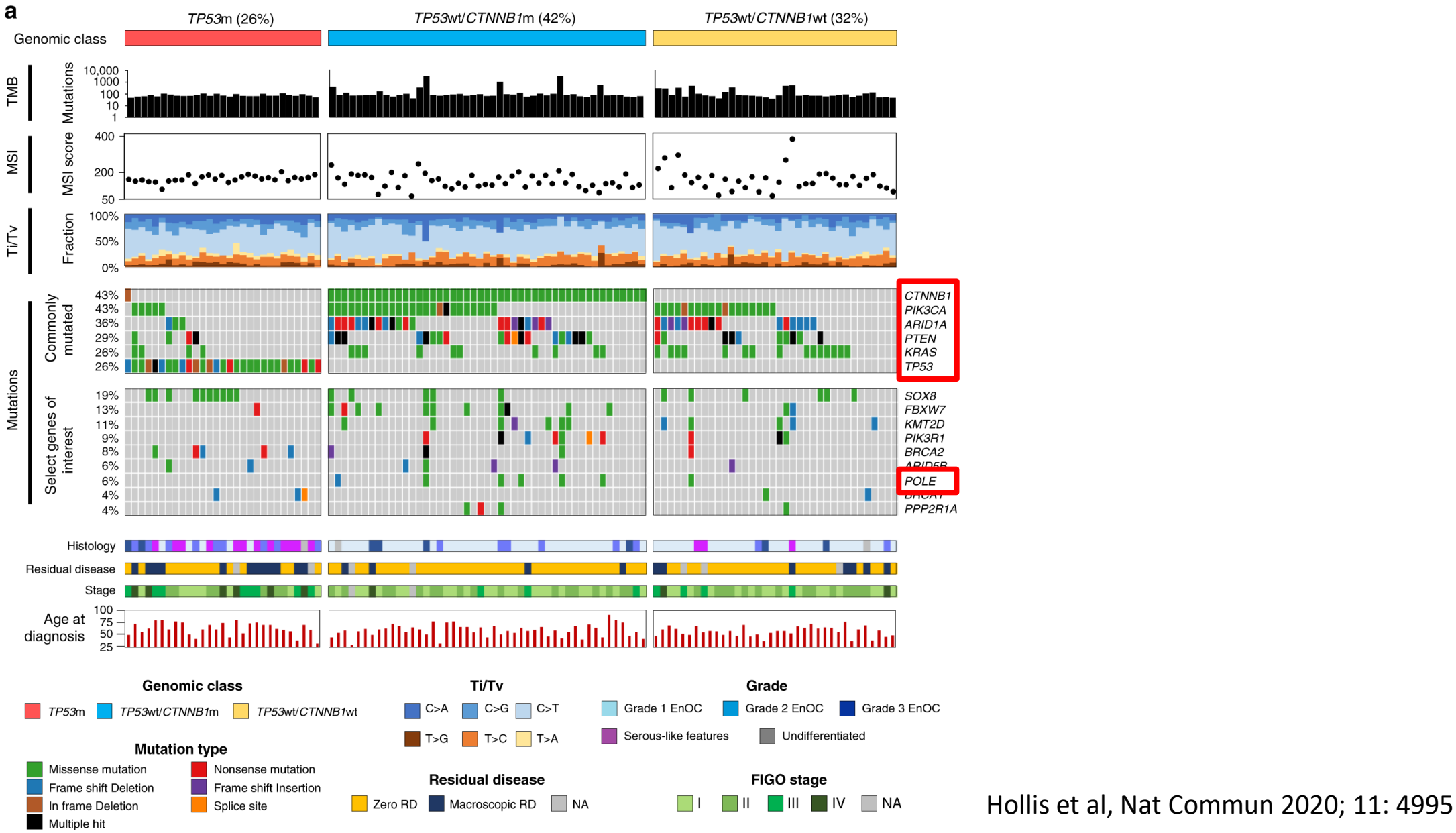

Kramer P, Talhouk A et al, Clin Cancer Res 2020; 26: 5400-5410

# Unsupervised clustering of endometrioid ovarian carcinomas by patterns of mutation



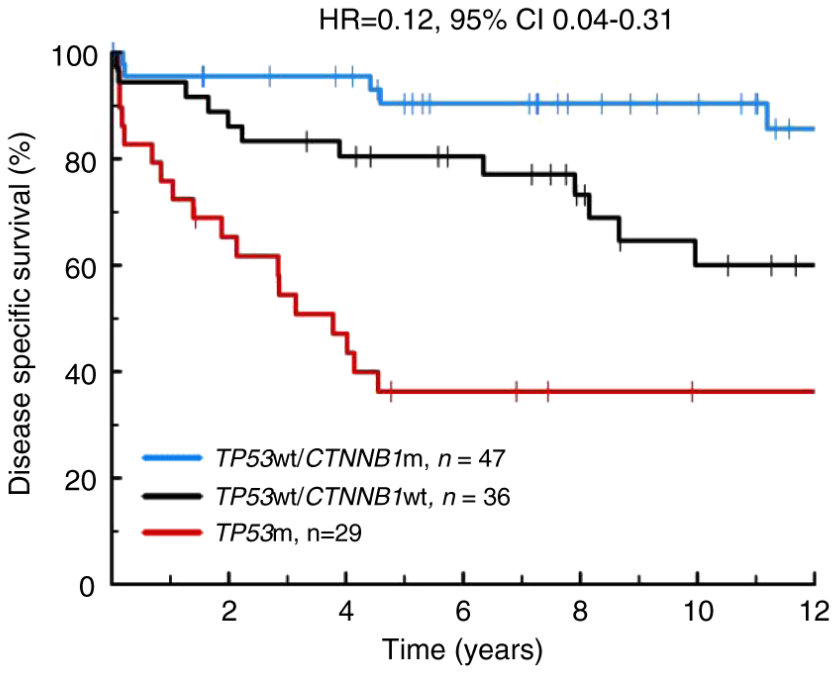

Hollis et al, Nat Commun 2020; 11: 4995

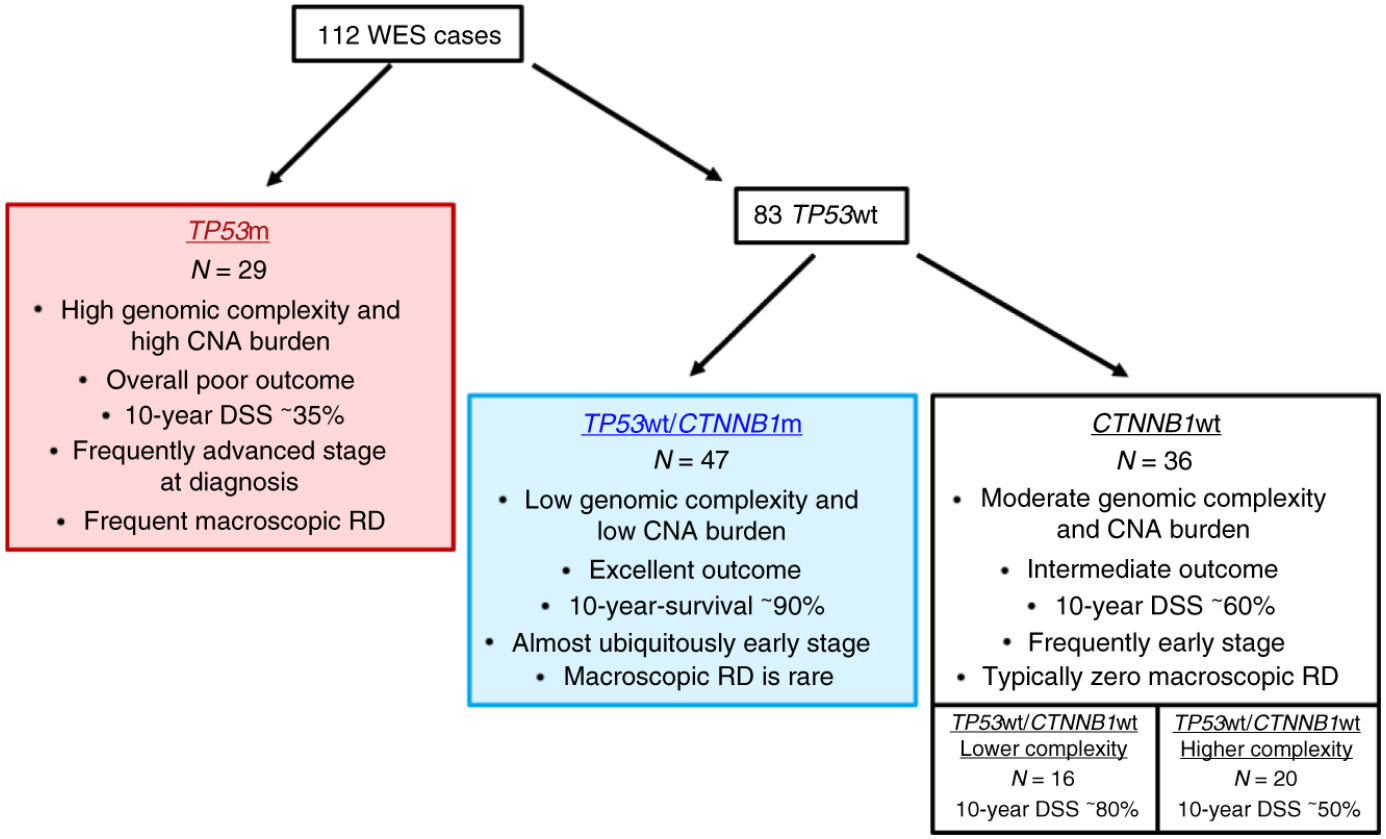
# Genomic characterisation of endometrioid ovarian carcinomas




Hollis et al, Nat Commun 2020; 11: 4995

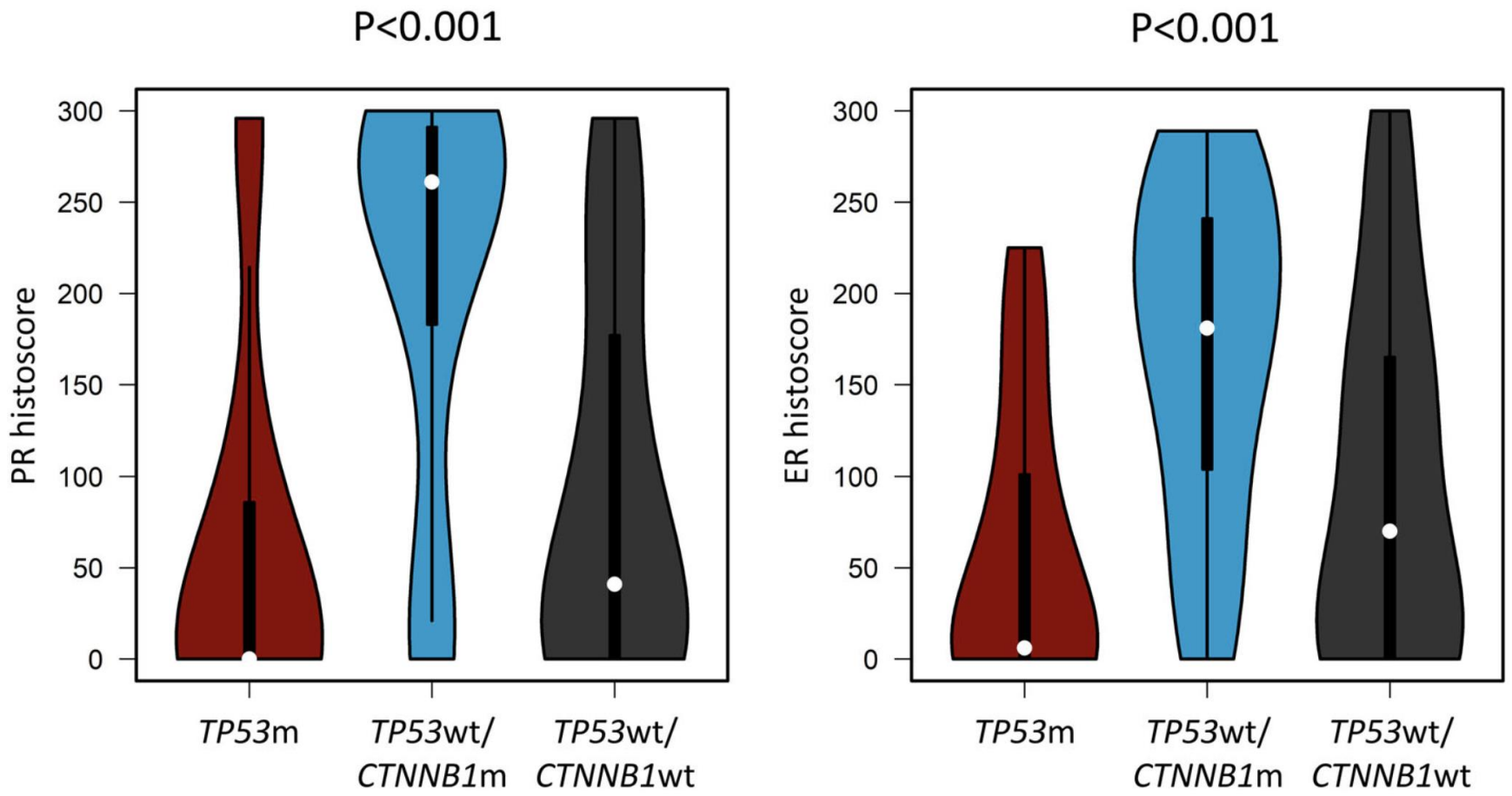
# Genomic subtypes of endometrioid ovarian carcinoma demonstrate distinct clinical behaviour



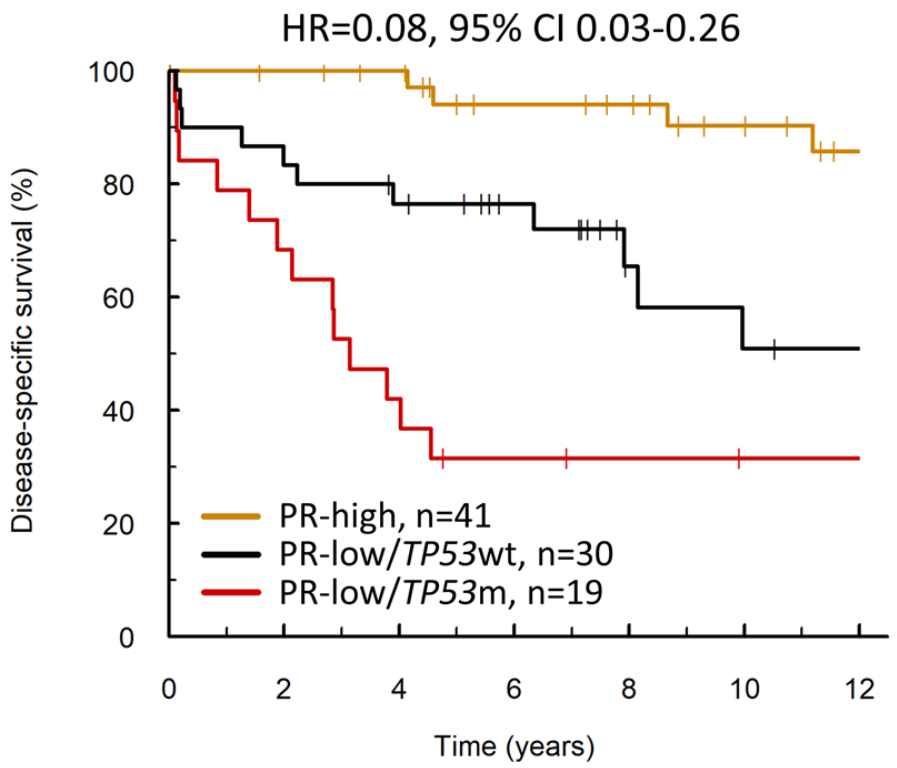

Hollis et al, Nat Commun 2020; 11: 4995

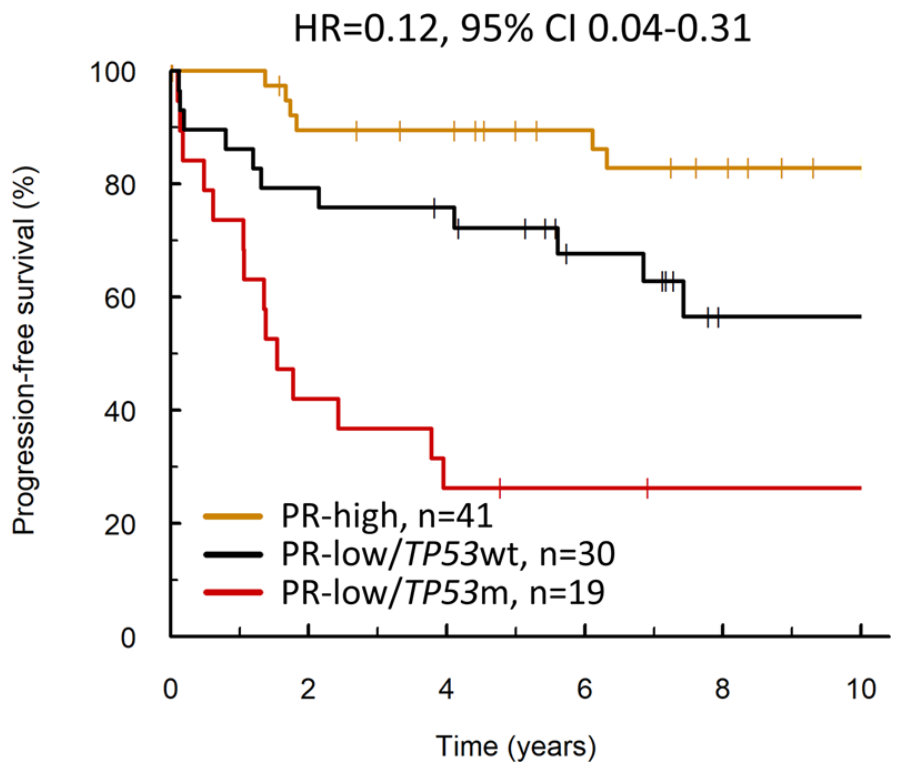
# Hormone receptor expression across genomic subtypes of endometrioid ovarian carcinoma




Hollis et al, npj Precision Oncology 2021; 5: 47

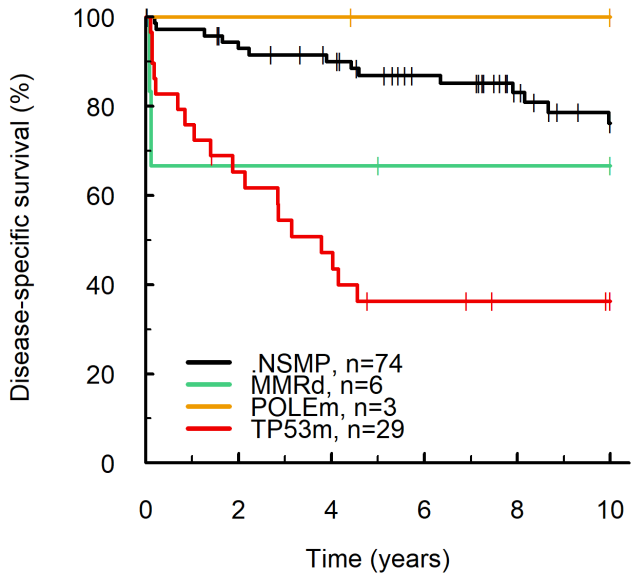
# Clinical outcome of endometrioid ovarian carcinoma cases defined by combined PR-based subtyping and *TP53* mutation status

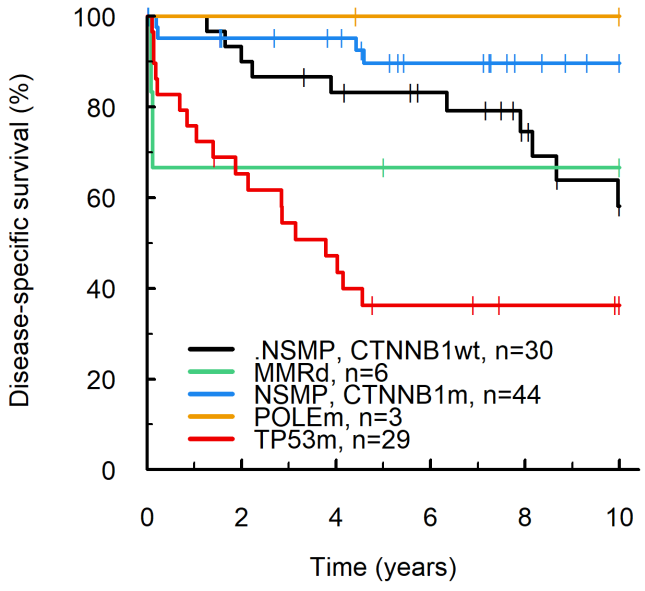


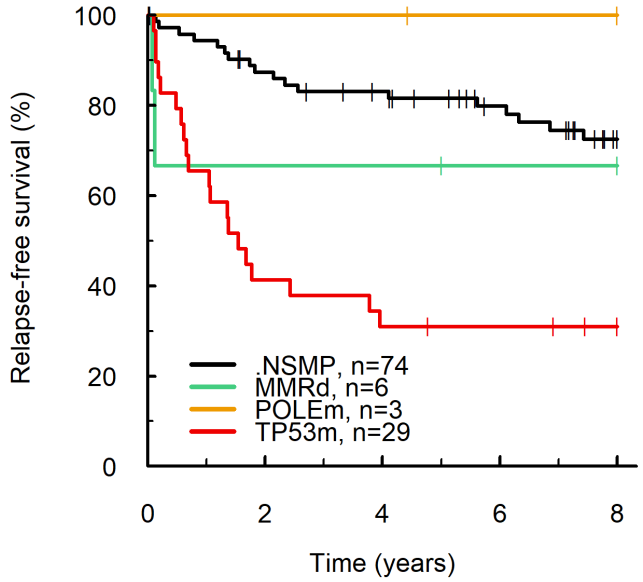

Hollis et al, npj Precision Oncology 2021; 5: 47

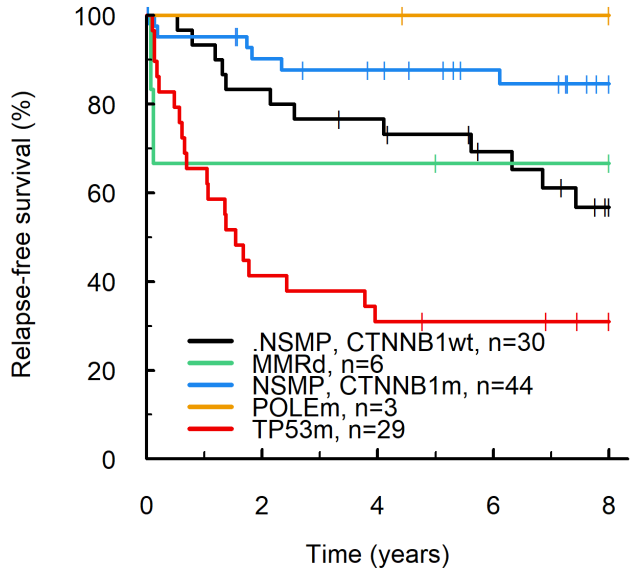
# PROMISE and PROMISE-plus




Univariable HR 0.29
95% CI 0.12-1.01
*CTNNB1* wt vs mutant



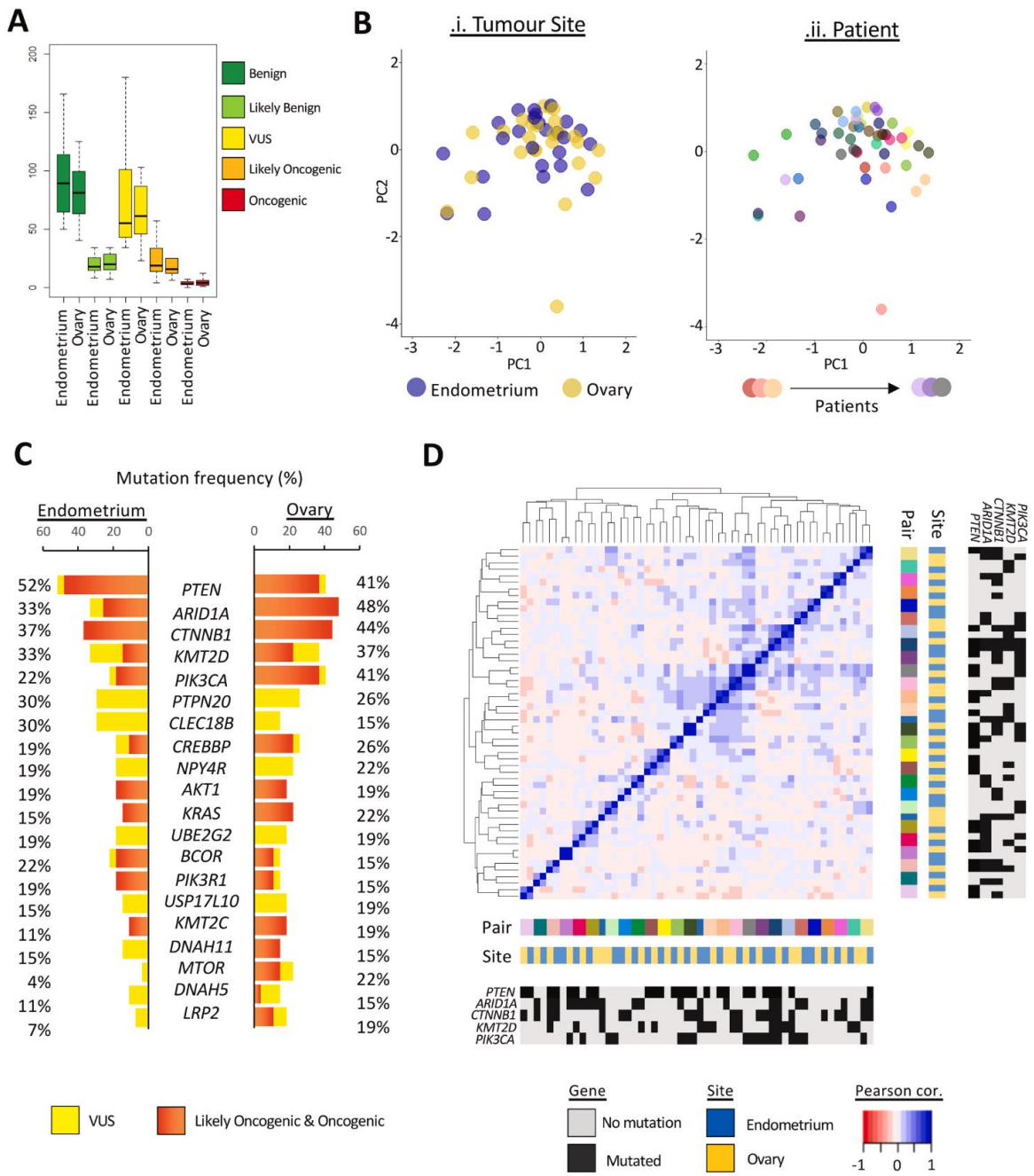

Univariable HR 0.34
95% CI 0.13-0.91
*CTNNB1* wt vs mutant

Hollis et al, unpublished

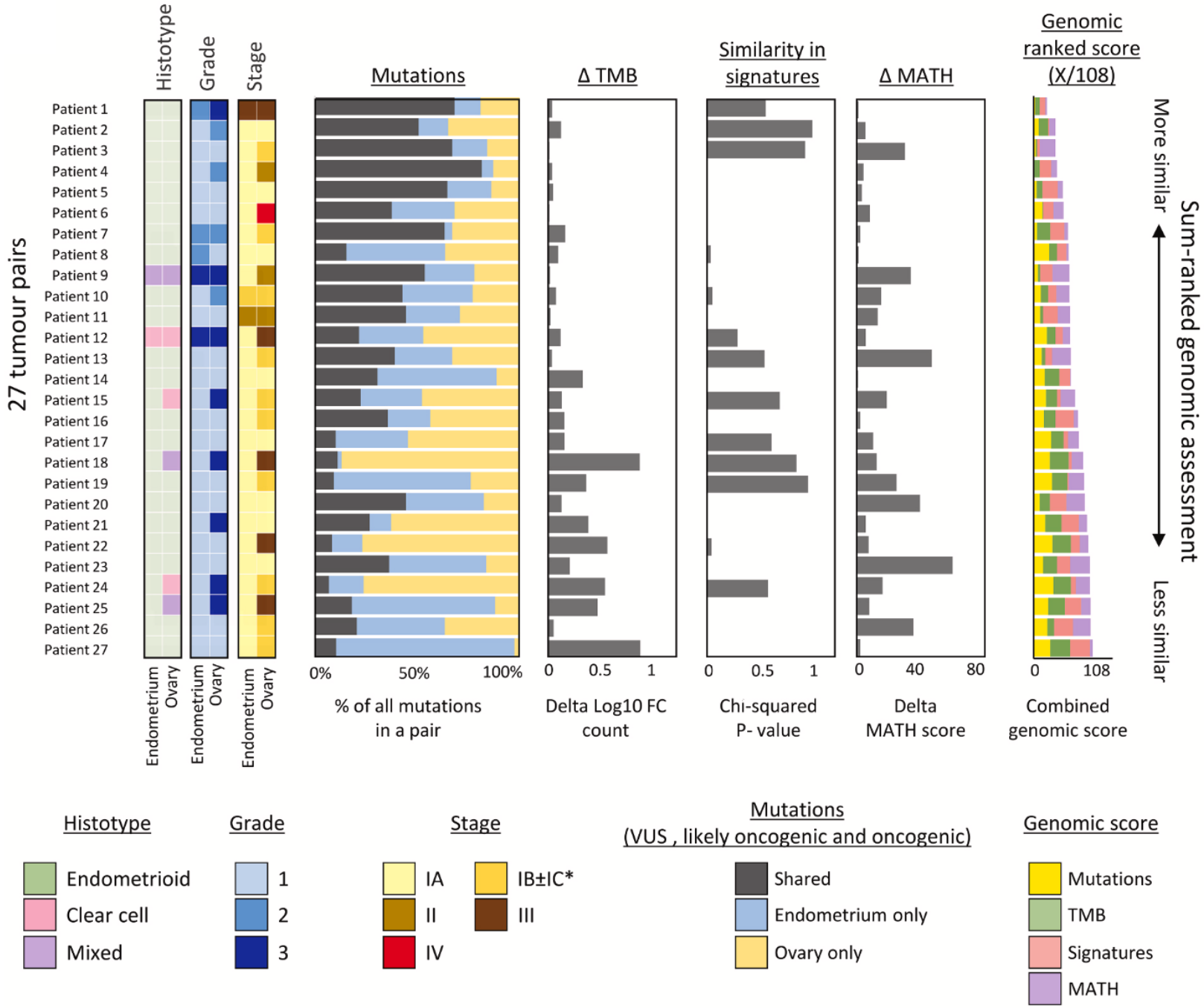
# Synchronous Ovarian and Endometrial Carcinomas

- ESGO/ESTRO/ESP guidelines
- 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’)

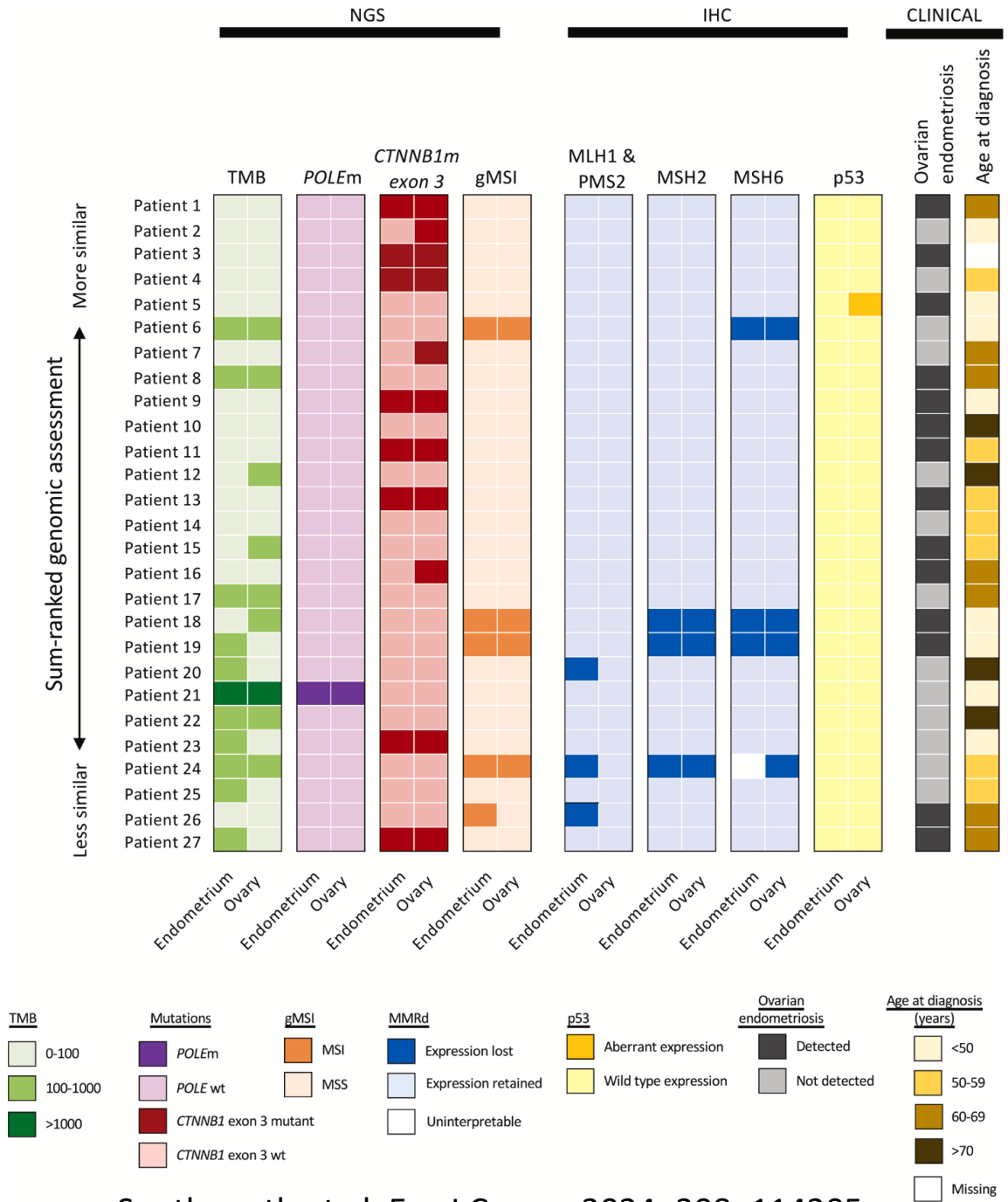
Concin N et al. Int J Gynecol Cancer 2021; 31, 12–39




Southworth et al, Eur J Cancer 2024; 208: 114205




Southworth et al, Eur J Cancer 2024; 208: 114205




Southworth et al, Eur J Cancer 2024; 208: 114205

# Synchronous Ovarian and Endometrial Carcinomas

- In our study, all paired tumours were genomically related
- This applied to endometrioid and clear cell carcinomas
- ProMisE parameters did not segregate according to genomic similarity
- This supports using a clinical risk strategy for the assessment of these tumours

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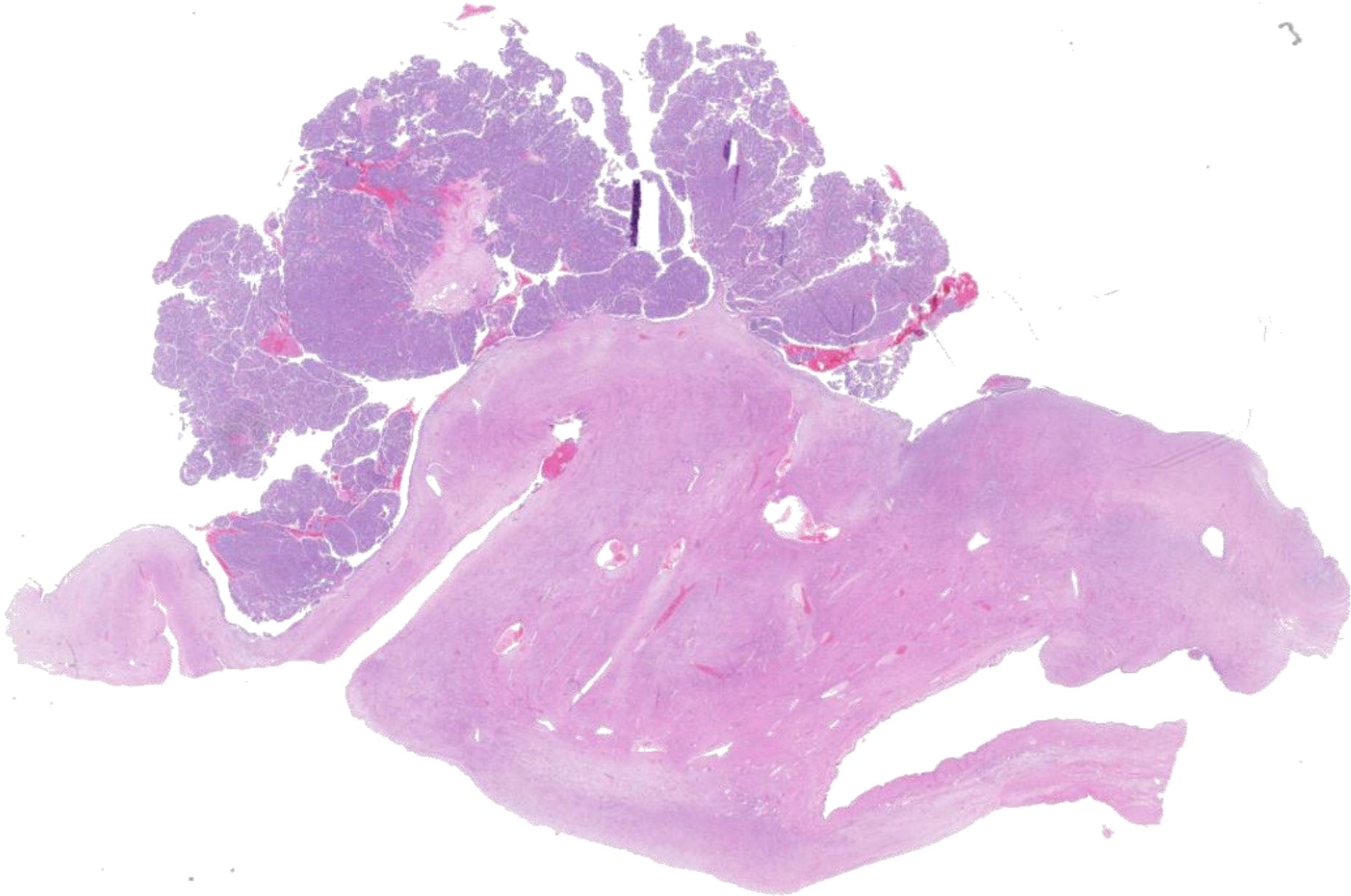
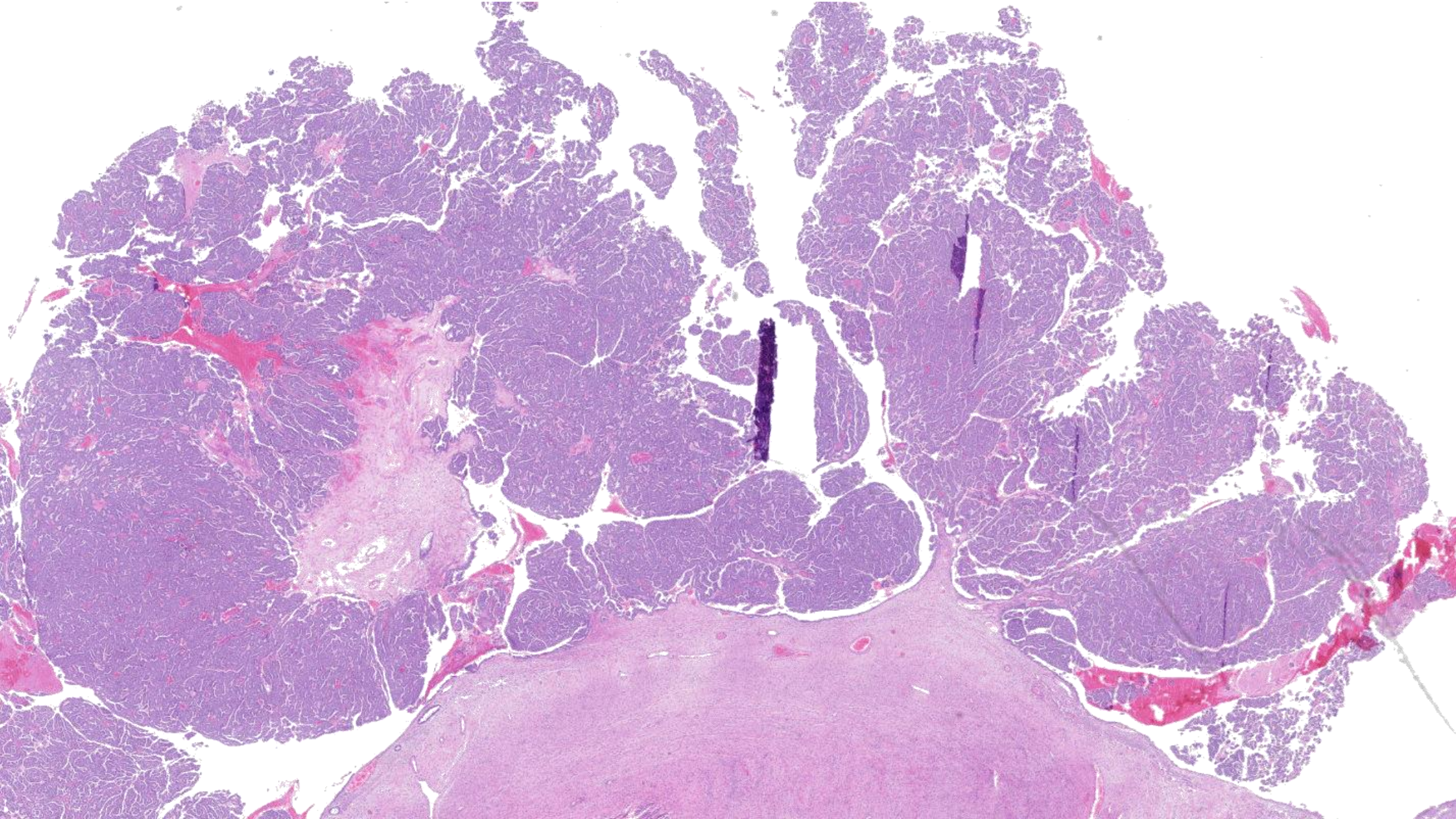
Concin N et al. Int J Gynecol Cancer 2021; 31, 12–39

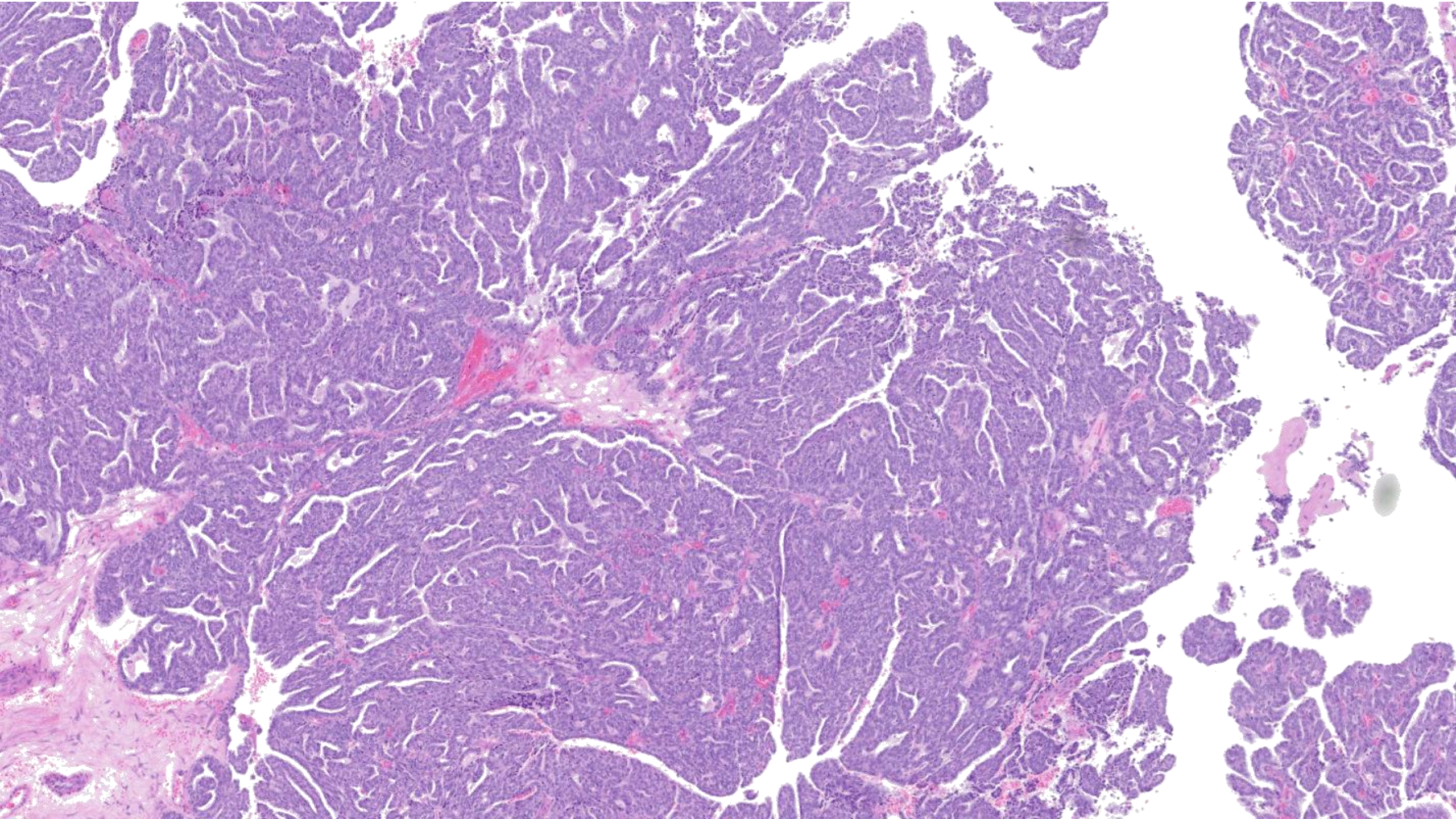
# Case

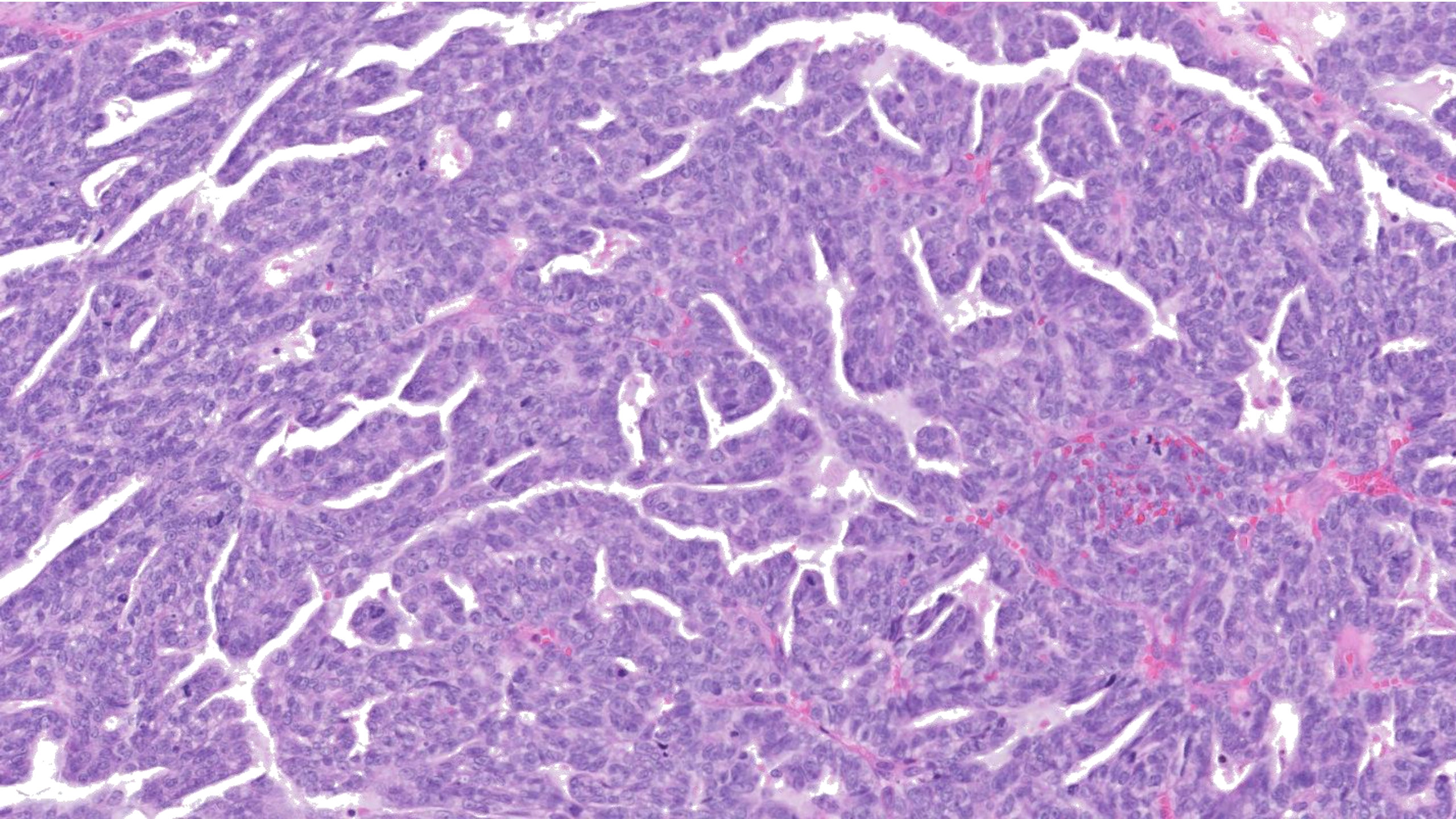
- Female aged 55 years
- TAH and BSO for 10 cm right adnexal mass

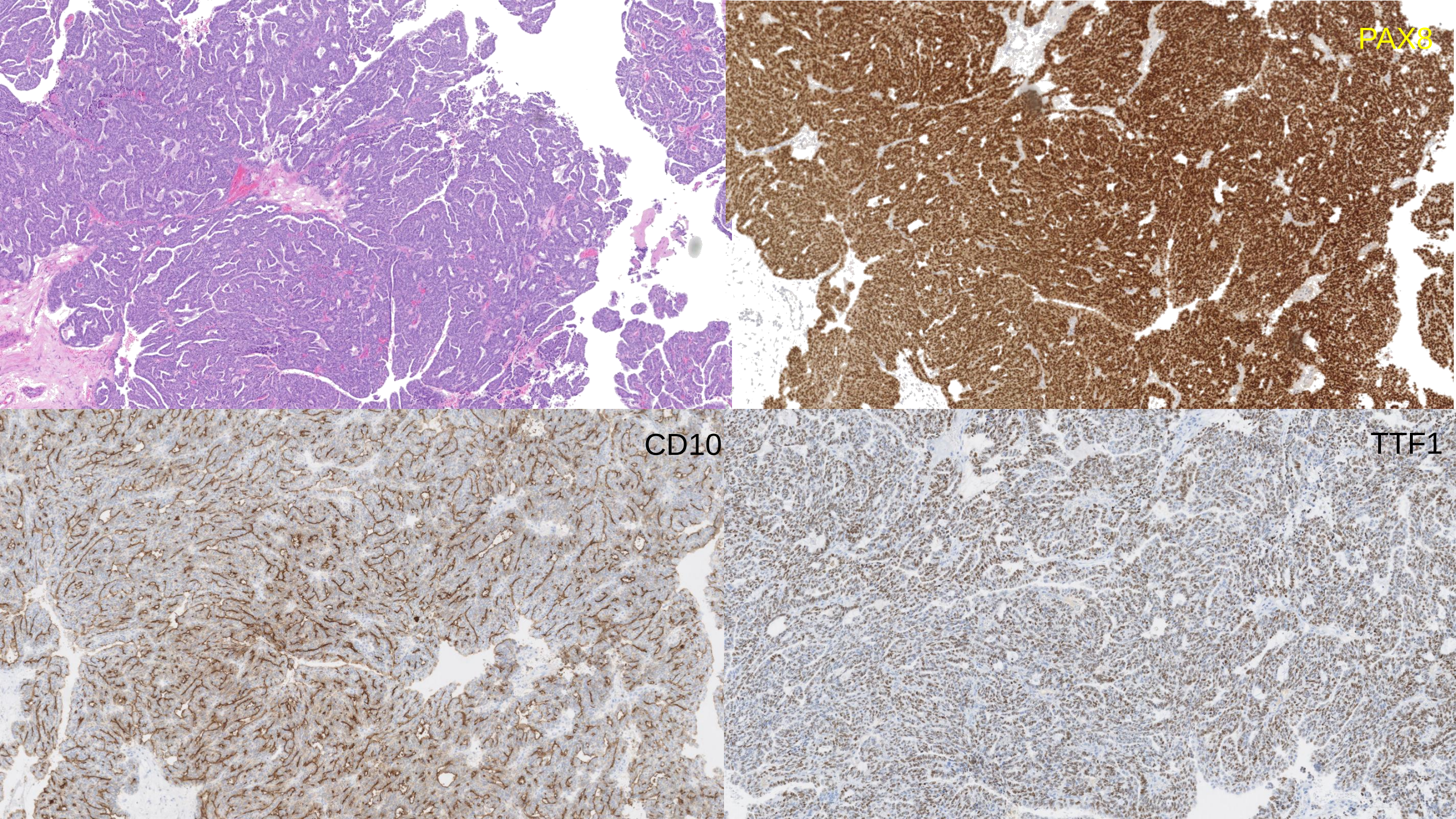
Case courtesy of Dr K Grondin, Québec, Canada

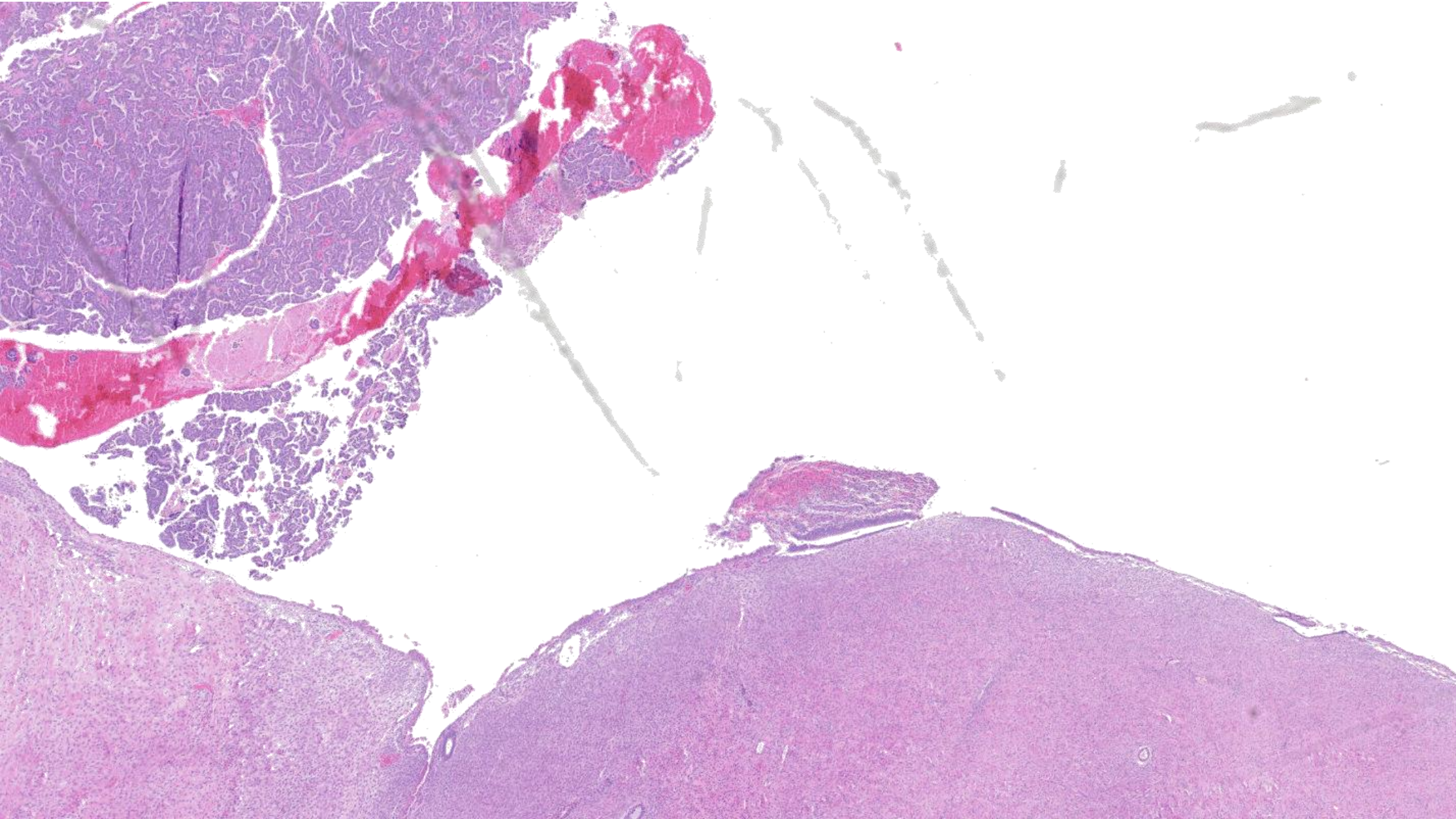


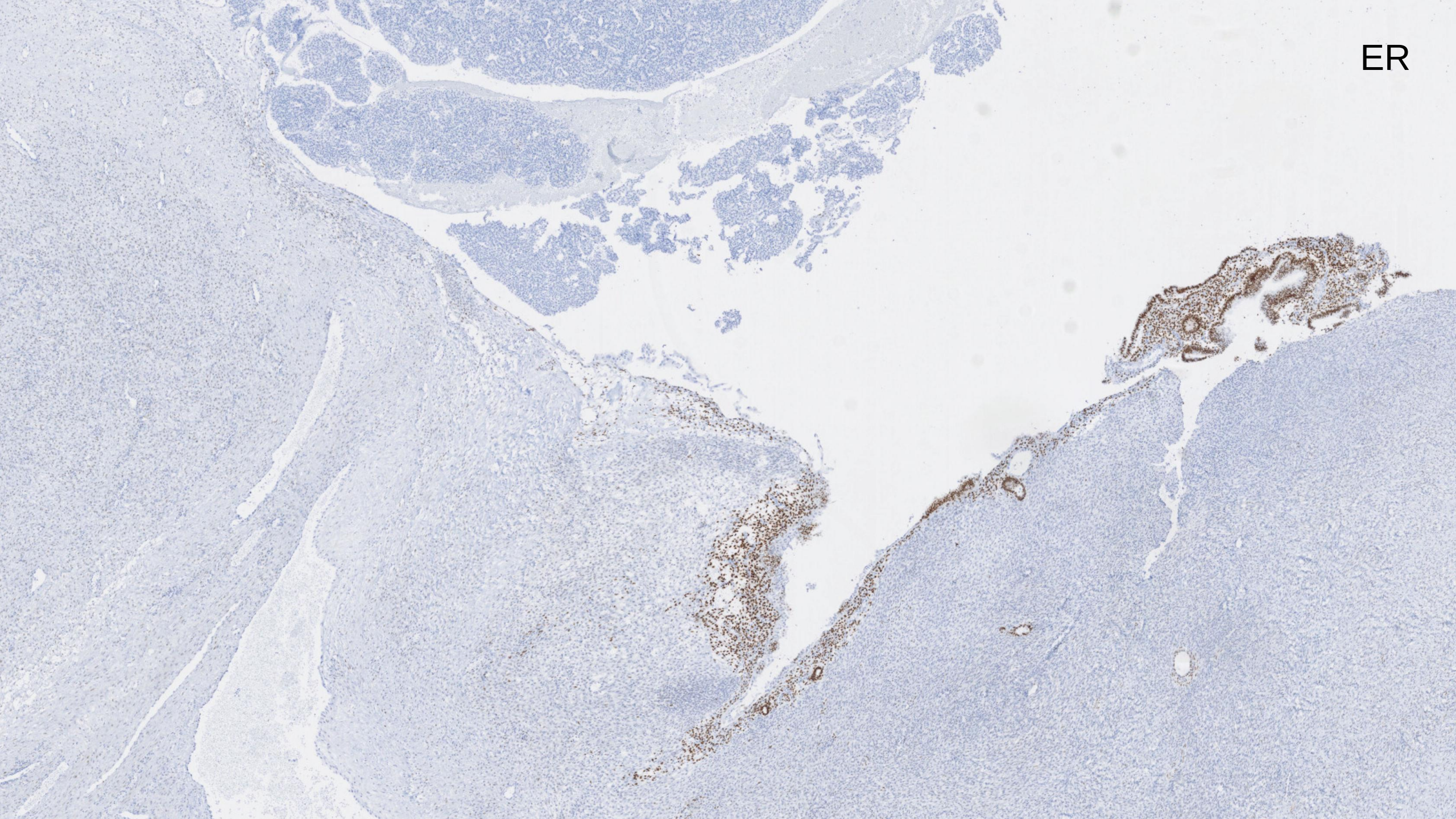






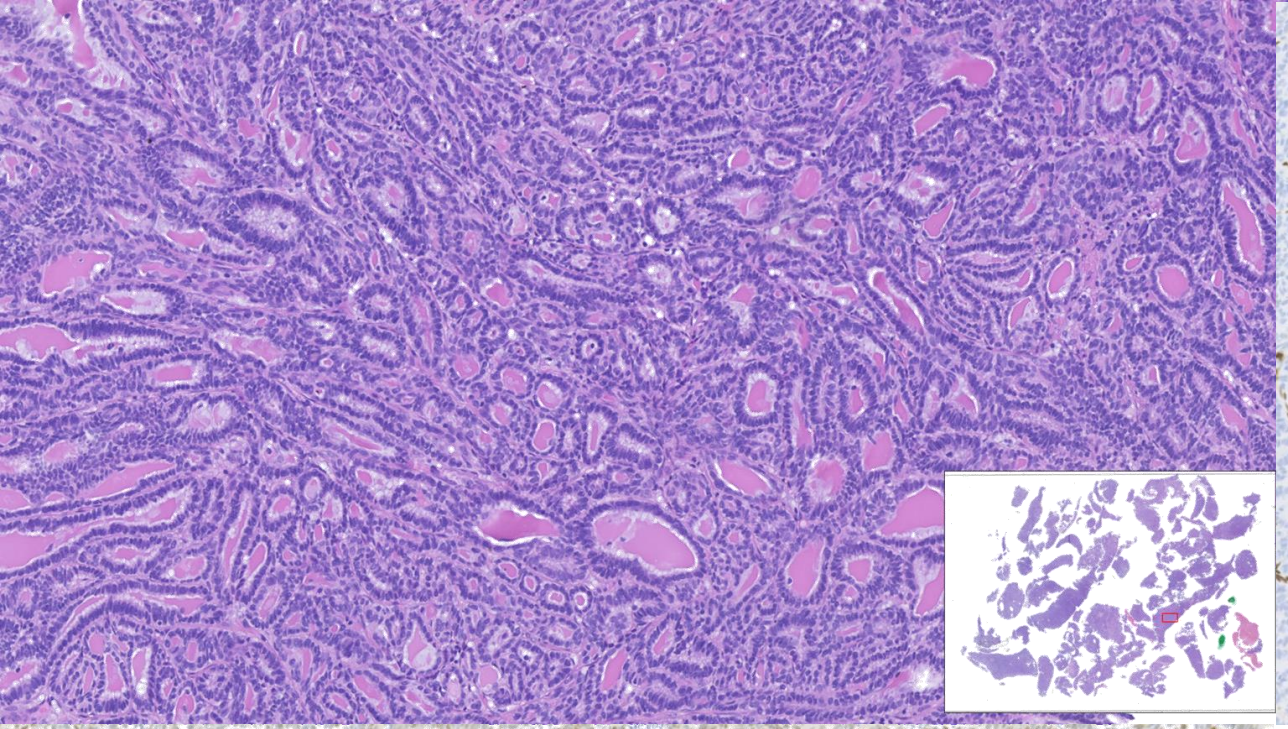

PAX8
CD10
TTF1

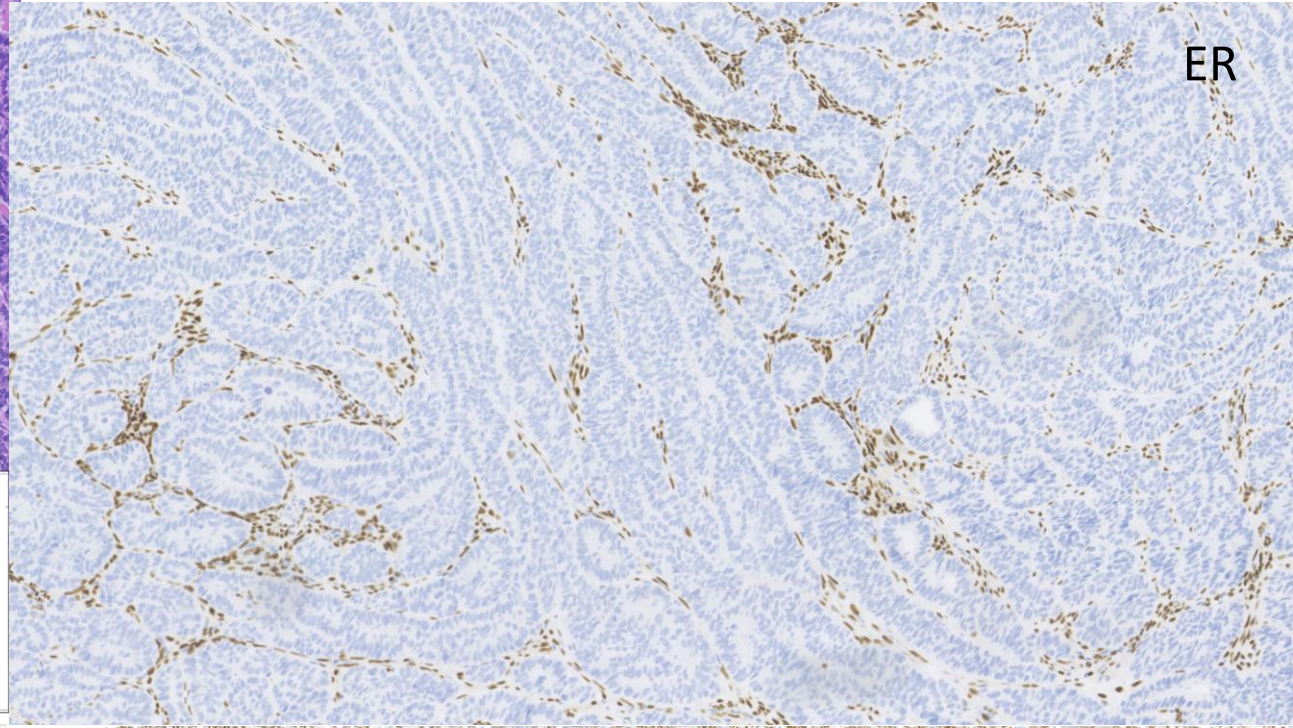



ER

# Diagnosis

## Mesonephric-like Adenocarcinoma of the Ovary

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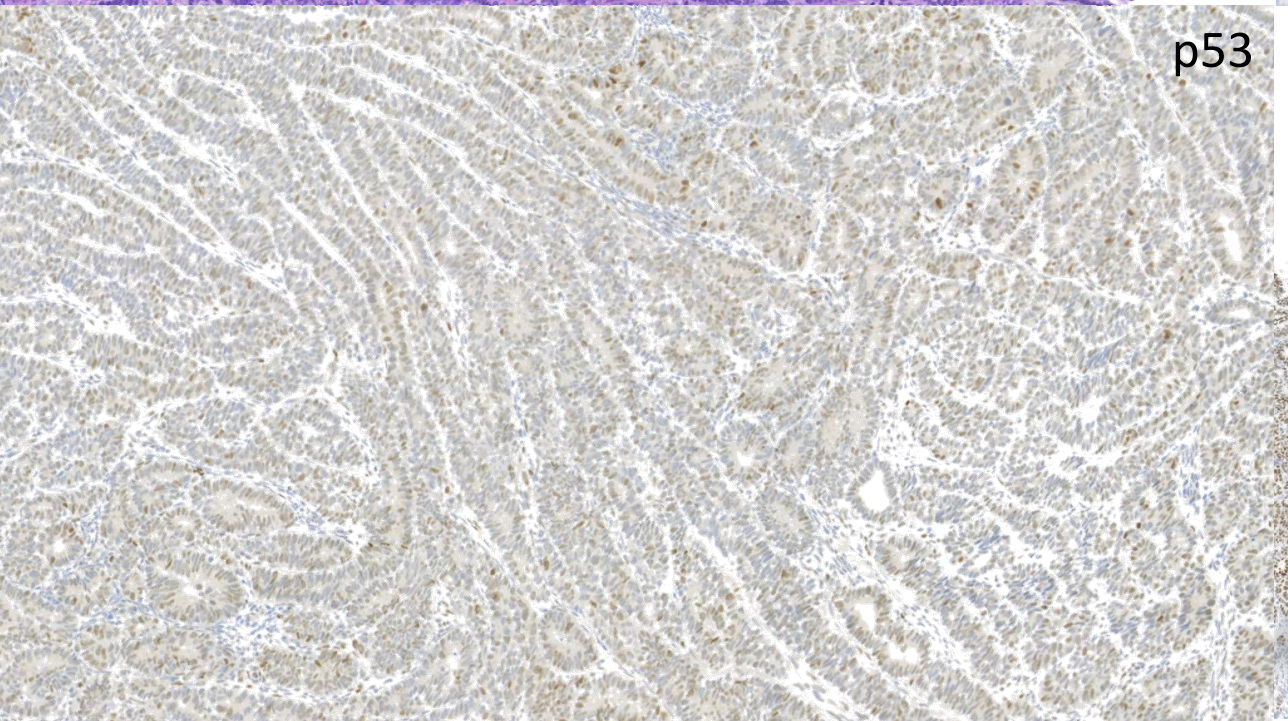
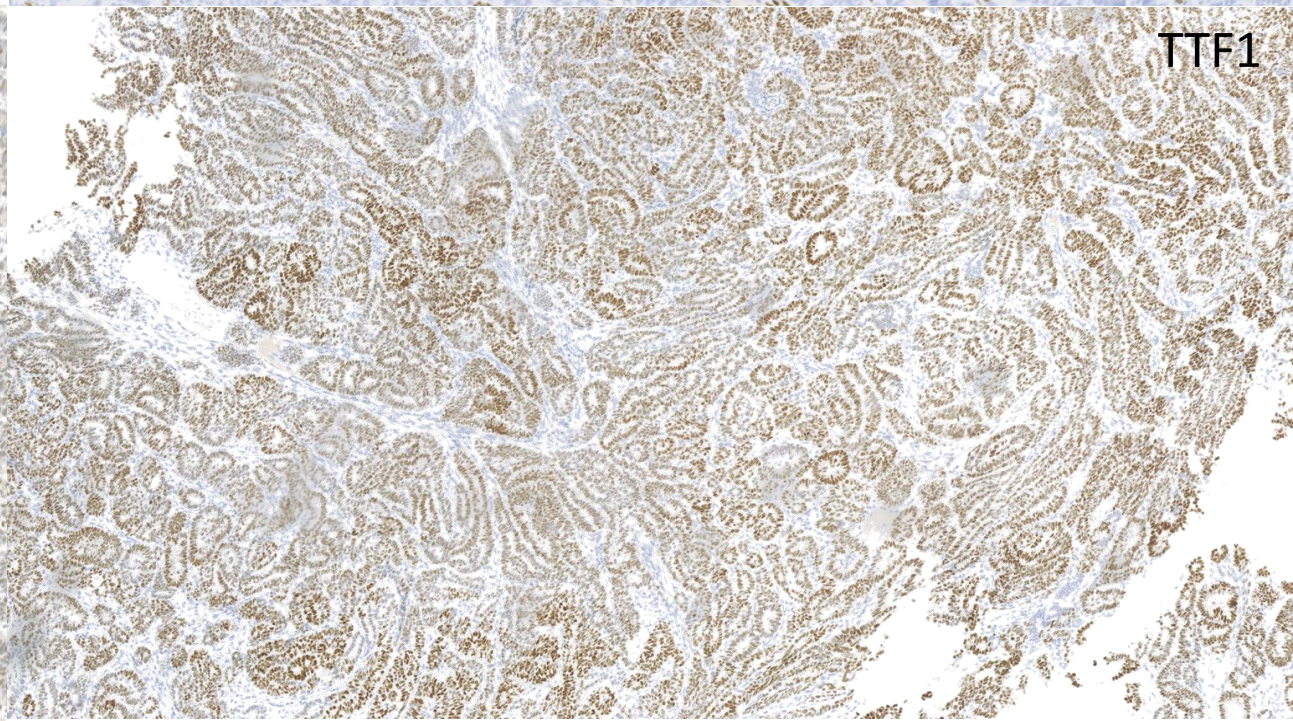

p53


TTF1

# Mesonephric-like Adenocarcinoma

- Adenocarcinoma resembling mesonephric carcinoma of the cervix
- Associated with endometriosis
- Typically ‘no specific molecular profile’ (NSMP), *KRAS* mutant, PAX8 positive, ER negative
- There may be an inverse relationship between GATA3 and TTF1 positivity
- Aggressive tumours with poor outcome

Pors J et al, Am J Surg Pathol 2018; 42: 1596-1606

Pors J et al, Am J Surg Pathol 2021; 45: 498-506

Bennett JA & Oliva E, Histopathology 2022; 81: 280-296

McCluggage WG, Adv Anat Pathol 2022; 29: 208-216

# Seromucinous tumours

- Classification
  - Mixed epithelial cystadenoma
  - Seromucinous borderline tumour
  - Seromucinous carcinoma
- Associated with endometriosis
- Seromucinous carcinoma deleted from WHO 2020 as considered a variant of endometrioid carcinoma
  - Supported by immunoprofile:
    - PAX8, ER/PR, CA125 positive; p53 wild type; WT1 negative

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

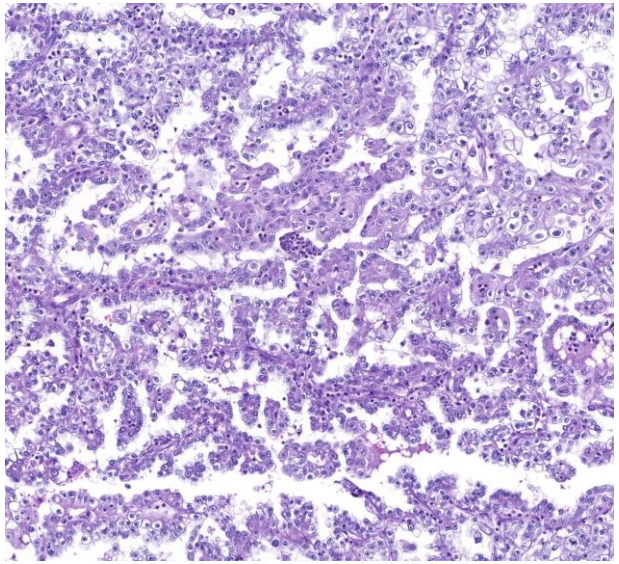
*Peter F. Rambau, MD,*† John B. McIntyre, PhD,‡ Jennifer Taylor, MD,§ Sandra Lee, MD,* Travis Ogilvie, MD,* Anna Sienko, MD,* Don Morris, MD,‡‖ Máire A. Duggan, MD,* W. Glenn McCluggage, MD,§ and Martin Köbel, MD**

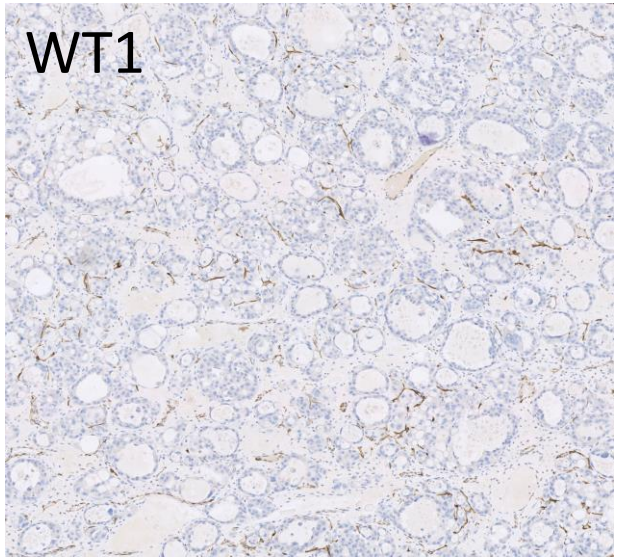
Am J Surg Pathol 2017; 41: 685-695

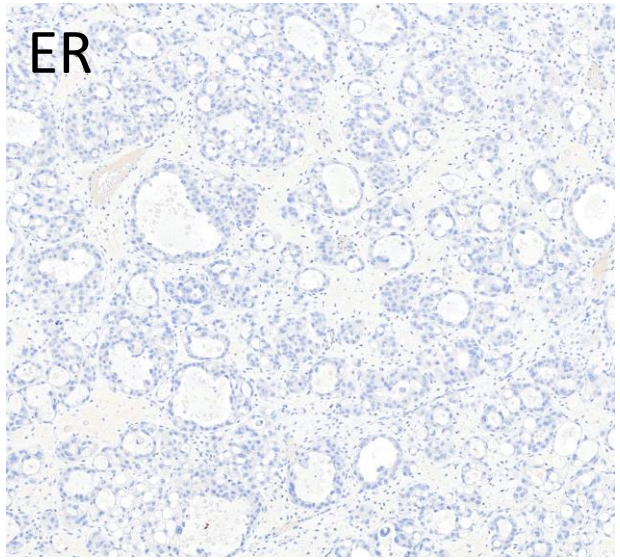
# Clear Cell Carcinoma

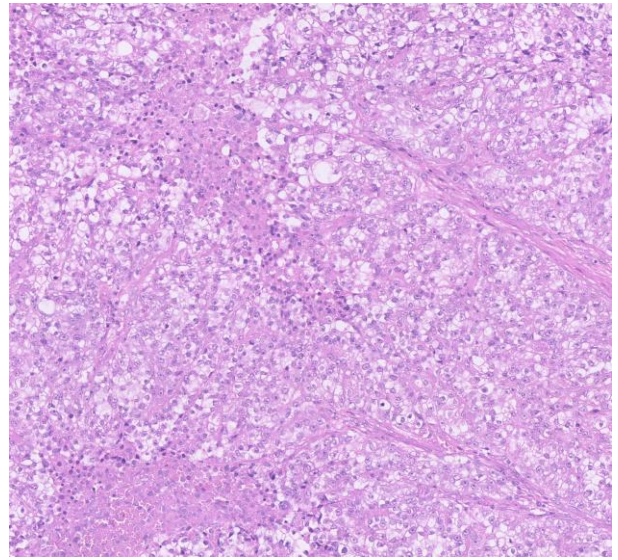
- Differential diagnosis
  - High-grade serous carcinoma with clear cells
  - Low grade serous carcinoma (when papillary)
  - Endometrioid carcinoma with secretory change or squamous differentiation
- Straightforward when classical
- Diagnosis supported by immunoprofile
  - WT1 negative, p53 wild type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

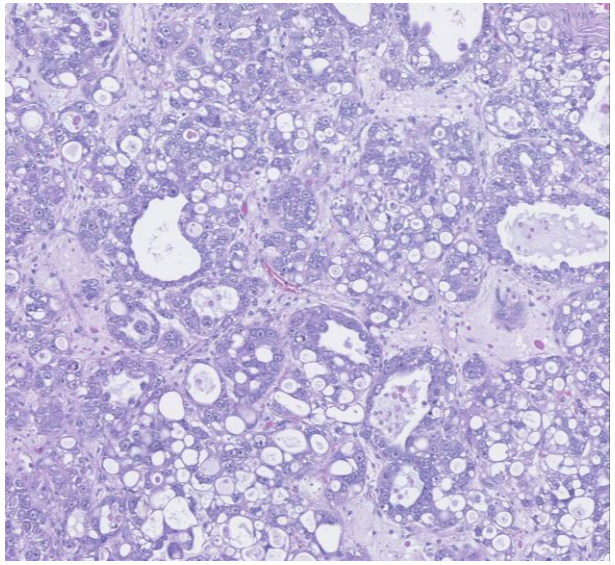
# Clear Cell Carcinoma

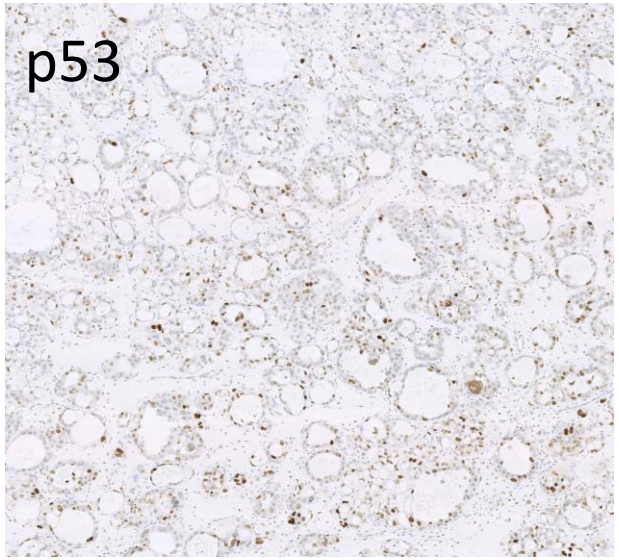


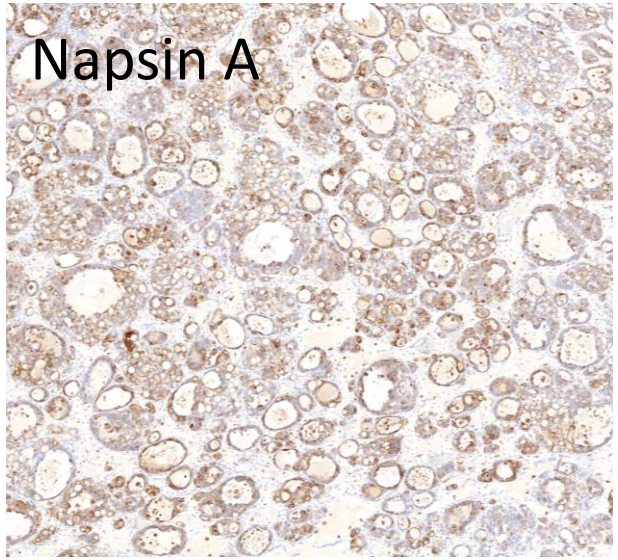


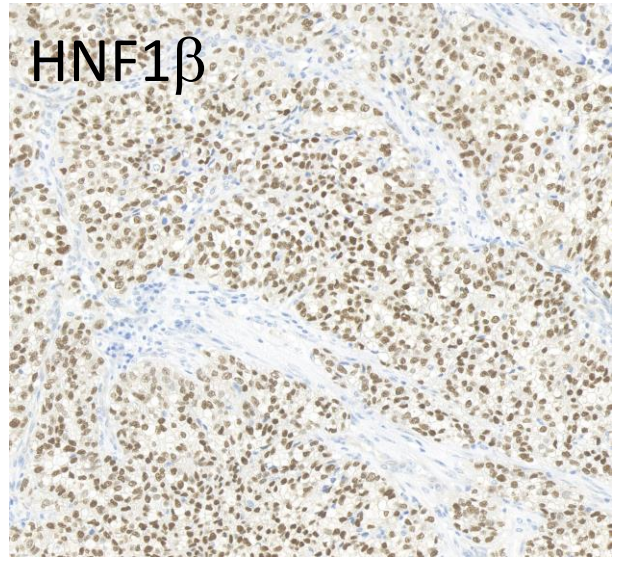





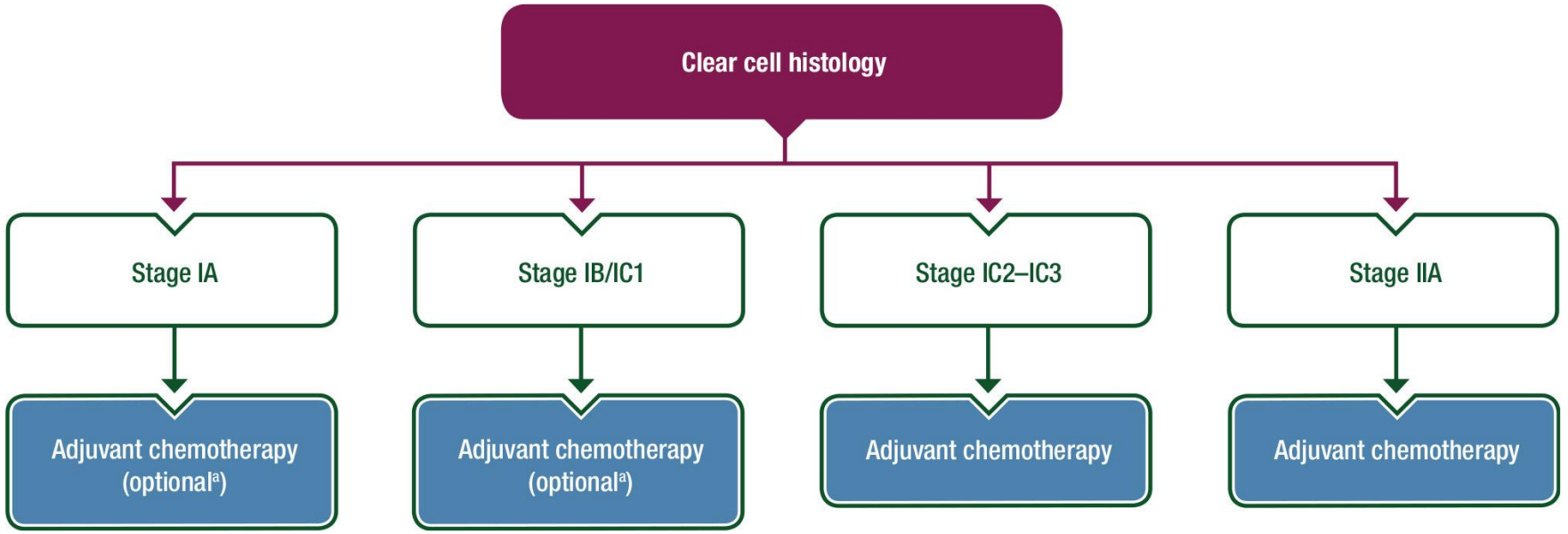


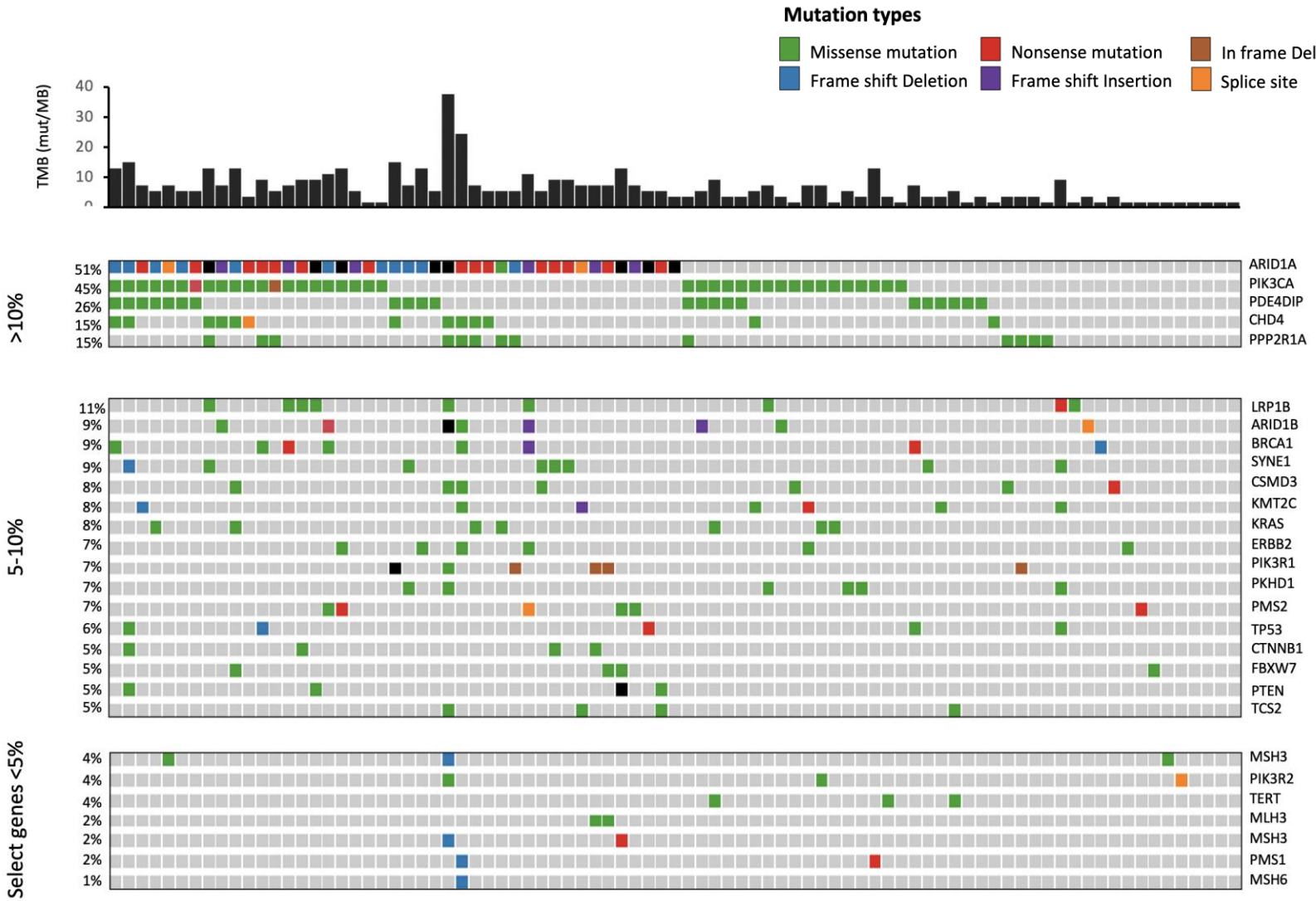
# Clear Cell Carcinoma

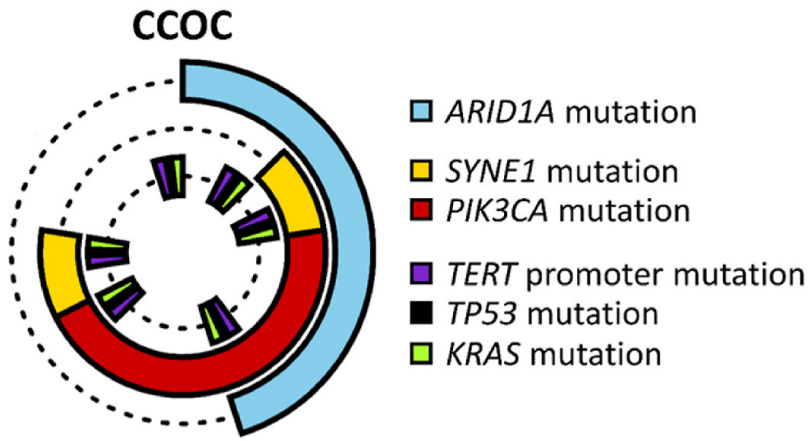
- Low stage disease has a good outcome
- High stage disease has a poor outcome




Colombo N et al. Ann Oncol 2019; 30: 672–705.
Iida Y et al. Int J Gynecol Cancer 2021; 31: 605–616

# Mutational Profile of Clear Cell Carcinoma

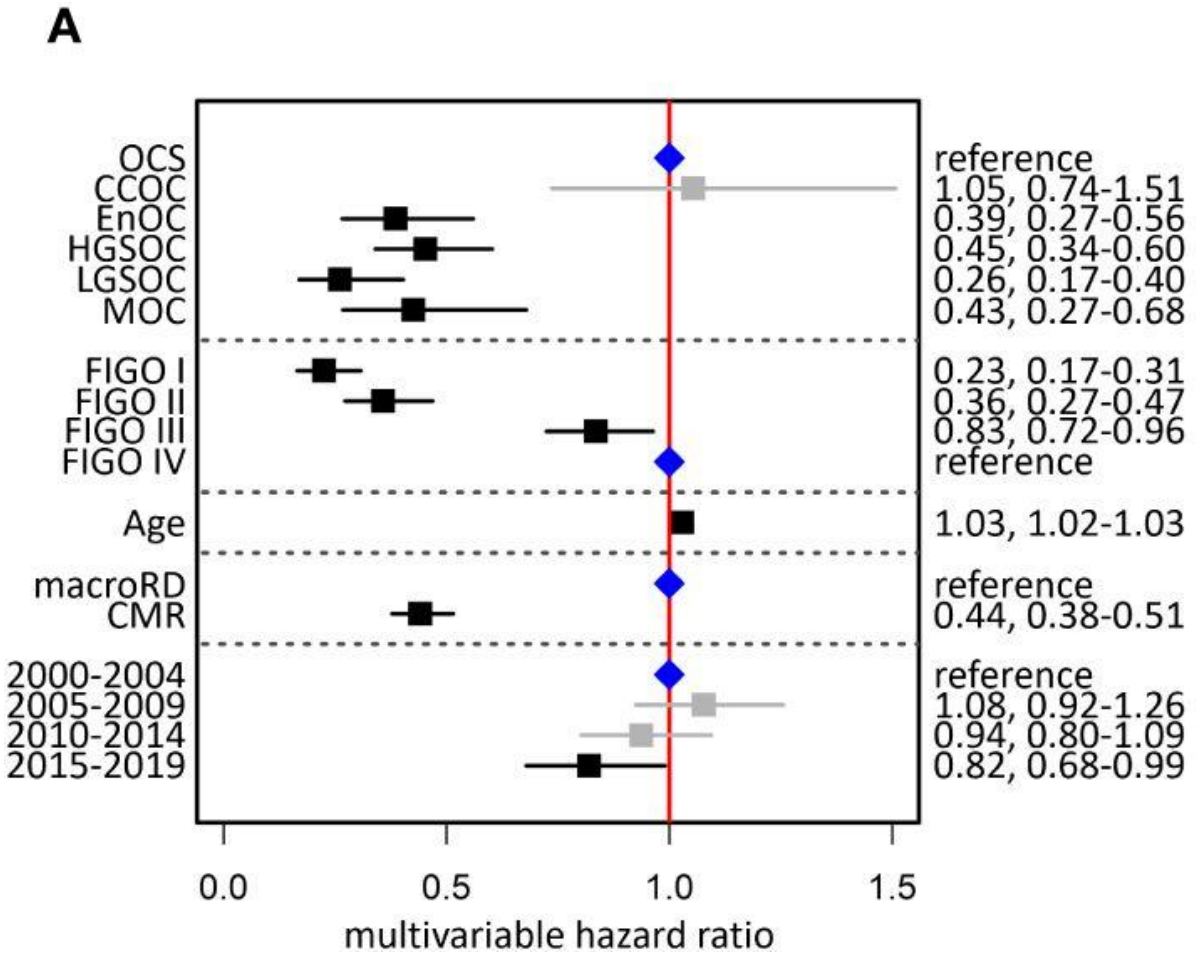


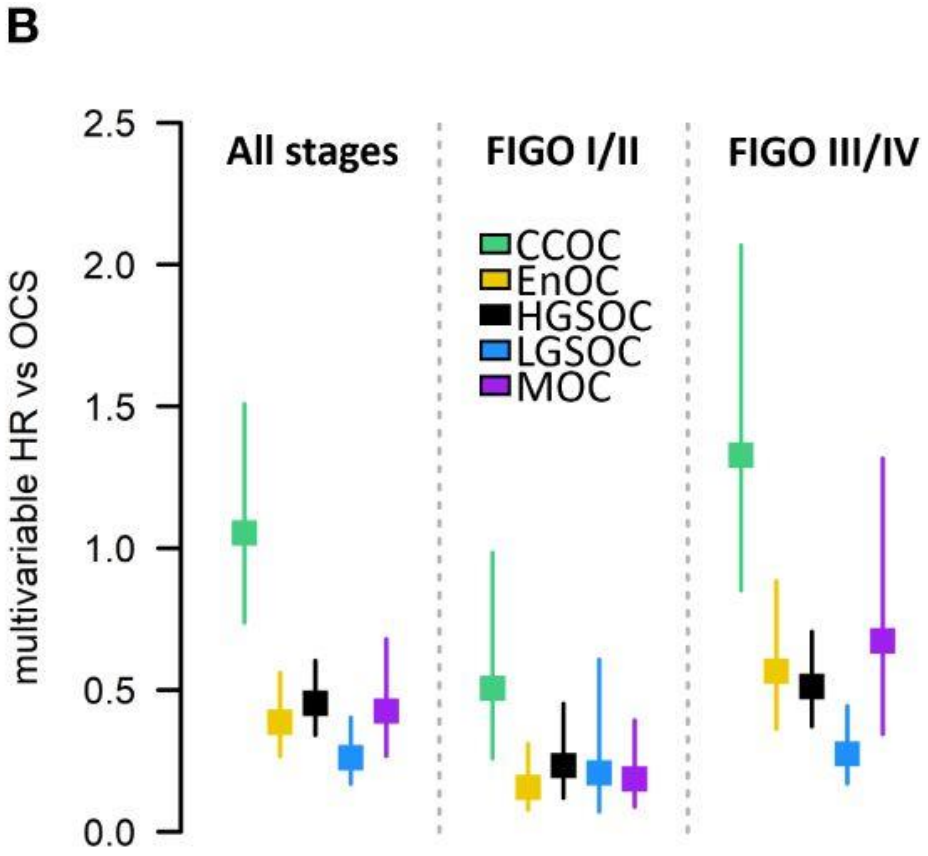




Hollis RL. Cancer Lett 2023; 555: 216057

Preliminary, unpublished

# Histotype and Outcome

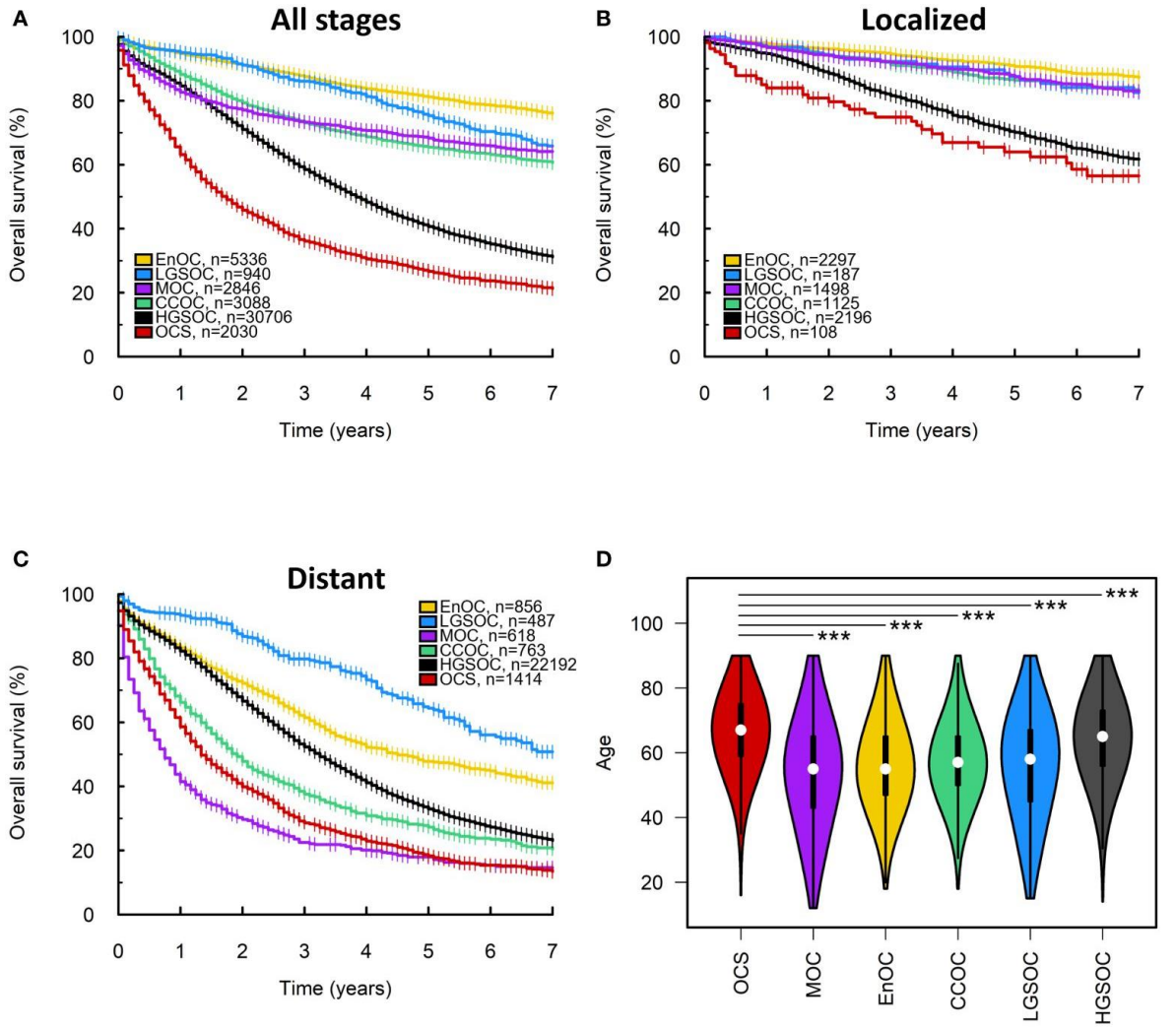


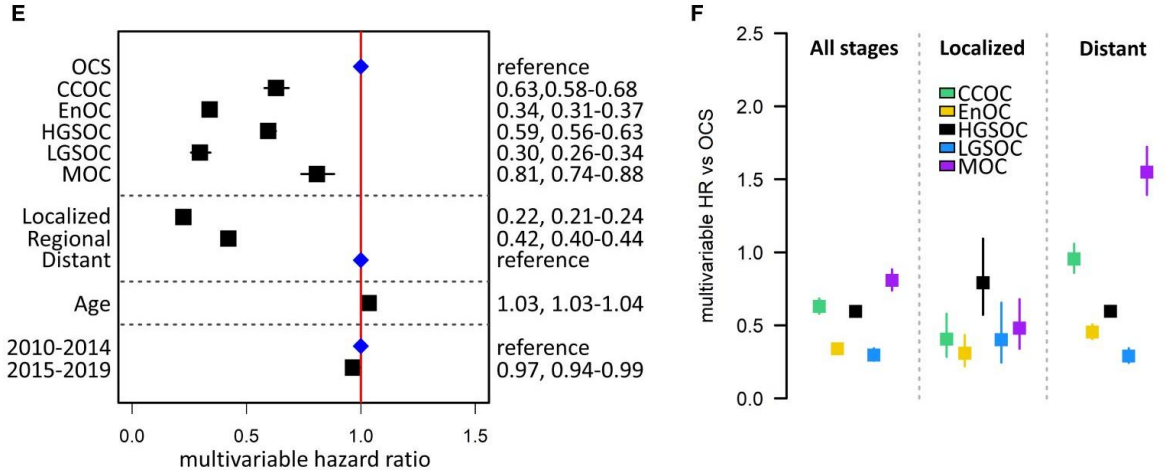




Scottish cohort, n = 2082

McFarlane et al, Front Oncol 2024; 14: 1399979

# Histotype and Outcome

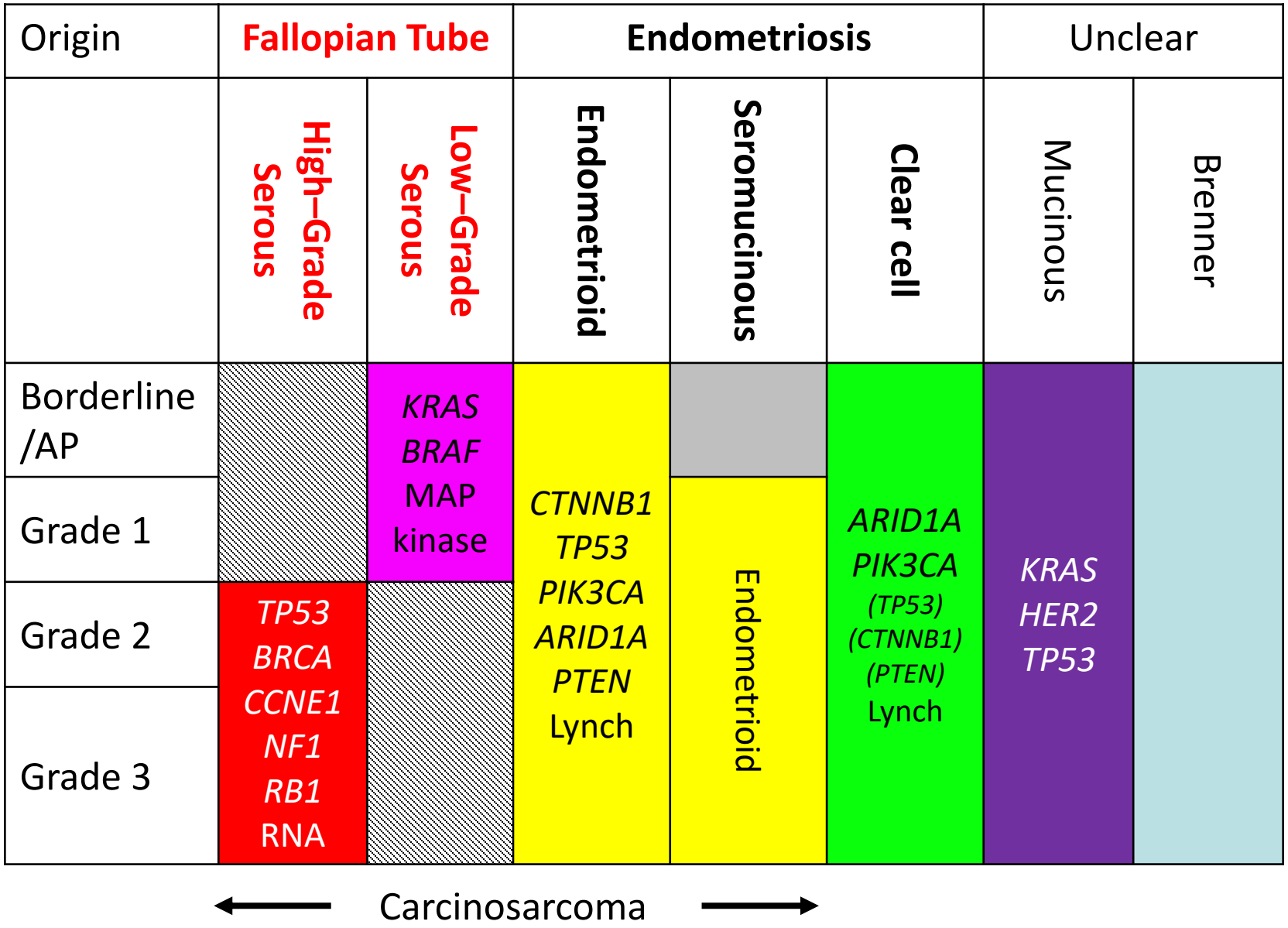



SEER cohort, n = 44946

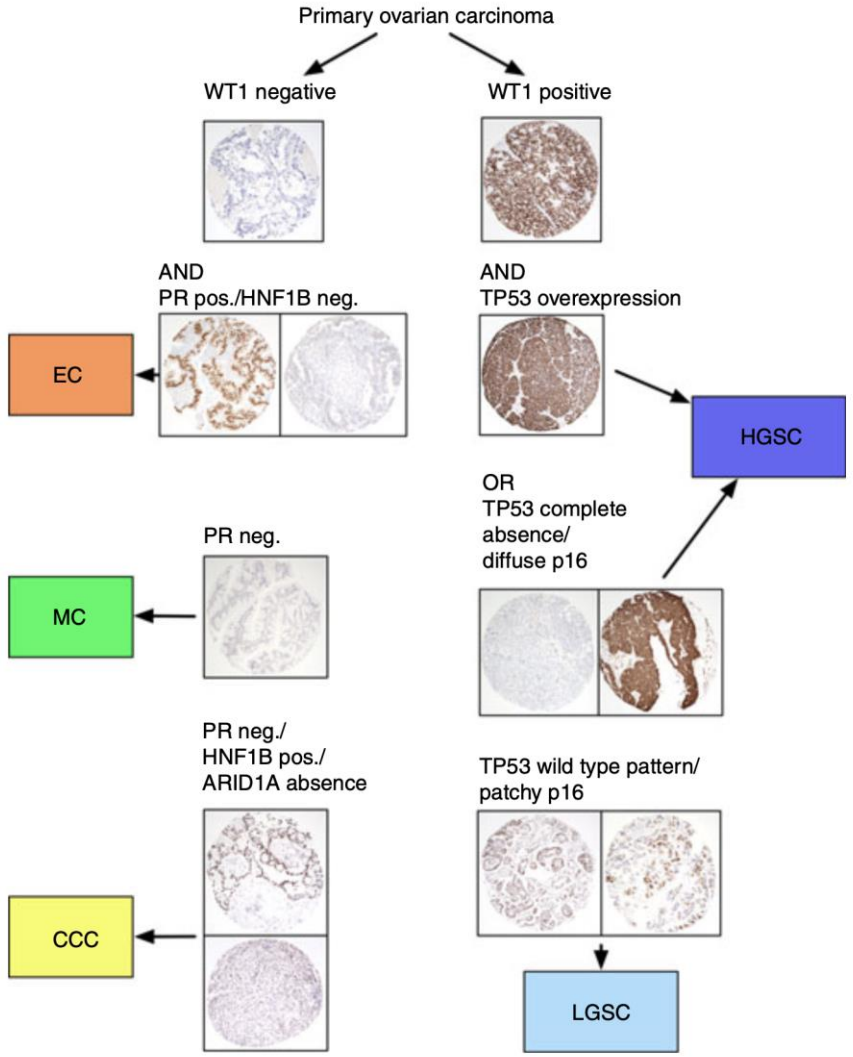
McFarlane et al, Front Oncol 2024; 14: 1399979

# Ovarian Epithelial Tumours



# 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



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