



AAPA 2026 **Annual Conference**

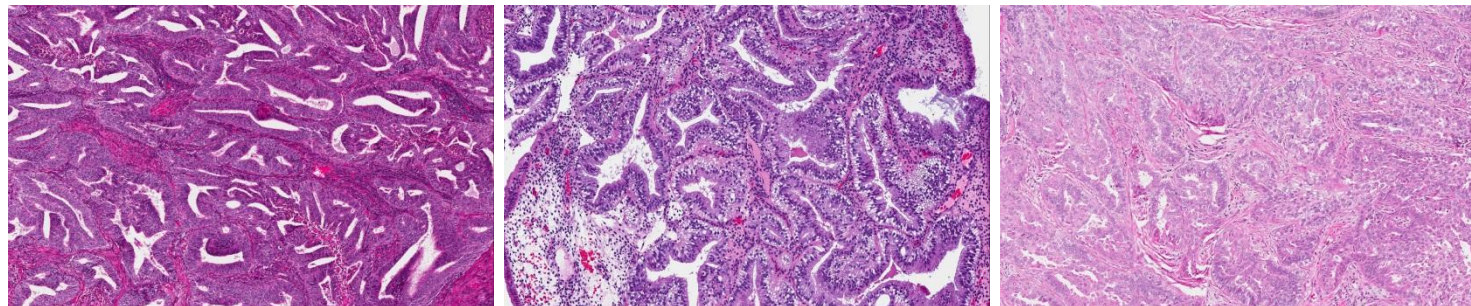
Here Comes the Sun:
Illuminating the Future of Pathology

September 13-17, 2026

Sheraton Phoenix Downtown • Phoenix, AZ

#AAPAfall26





Molecular Classification of Endometrial Carcinomas: How and When?

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Disclosure

- I have no financial disclosure!

Outlines

- Introduction of The TCGA molecular classification
- The 2023 FIGO stage of EM CA: what has changed?
- How Mayo Clinic incorporate molecular classification and the new FIGO stage of EM CA
- Use several cases to illustrate the importance of molecular classification
- Future perspectives and conclusions

WHO 2020 Endometrial Carcinoma Classification

- Endometrioid
- Serous
- Clear cell
- Undifferentiated/De-differentiated
- Carcinosarcoma
- Mixed carcinomas
- Others: mesonephric-like, gastric-type
mucinous, squamous carcinoma



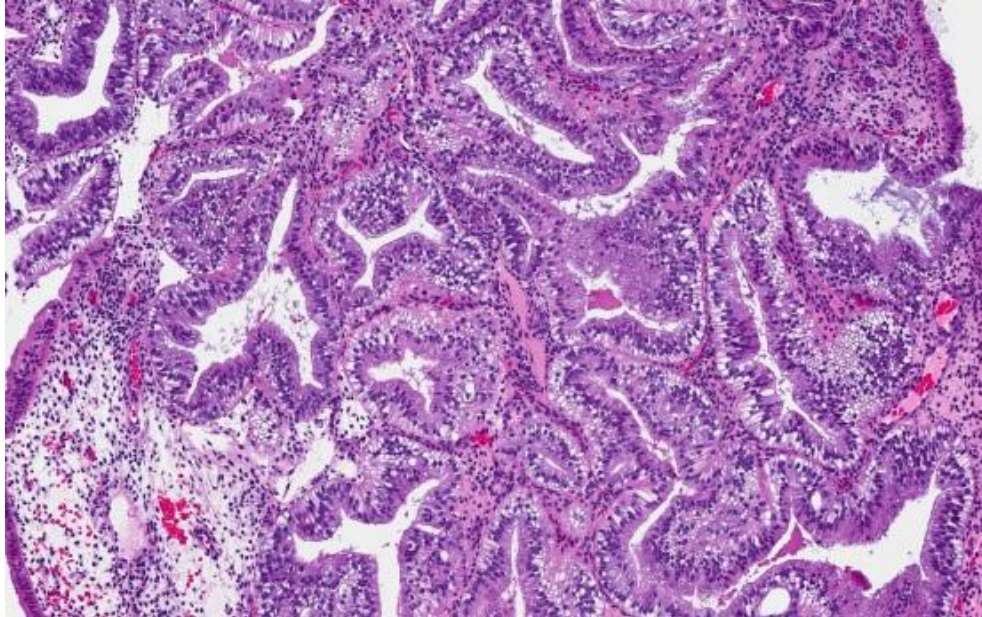
High grade

Conventional prognostic Risk Groups

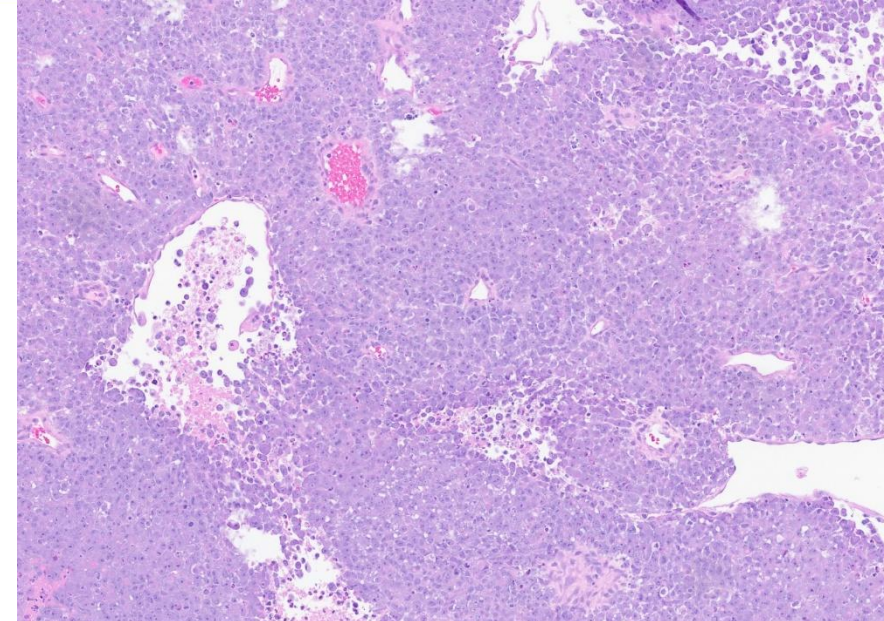
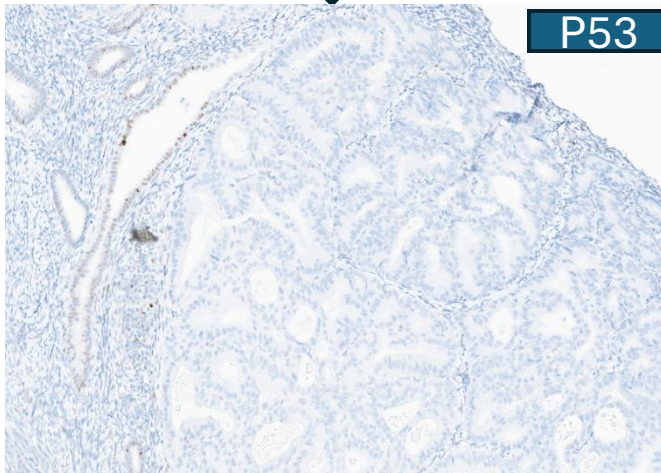
Risk Group	Molecular Classification Unknown
Low	• Stage IA endometrioid + low grade +LVSI negative or focal
Intermediate	• IA endometrioid + high grade + LVSI (- or focal) • IA non-endometrioid without invasion • IB endometrioid + low grade + -/focal LVSI
High-Intermediate	• I endometrioid + extensive LVSI • IB endometrioid + high grade regardless of LVSI • Stage II
High	• Stage III-IVA • Stage II-IVA non-endometrioid + myometrial invasion

Problems solely rely on histological diagnosis

- High inter-observer variation on high grade EC
- Histological subtypes in EC do not consistently predict clinical outcome
 - Histologically high grade, but clinically behaves like low-grade



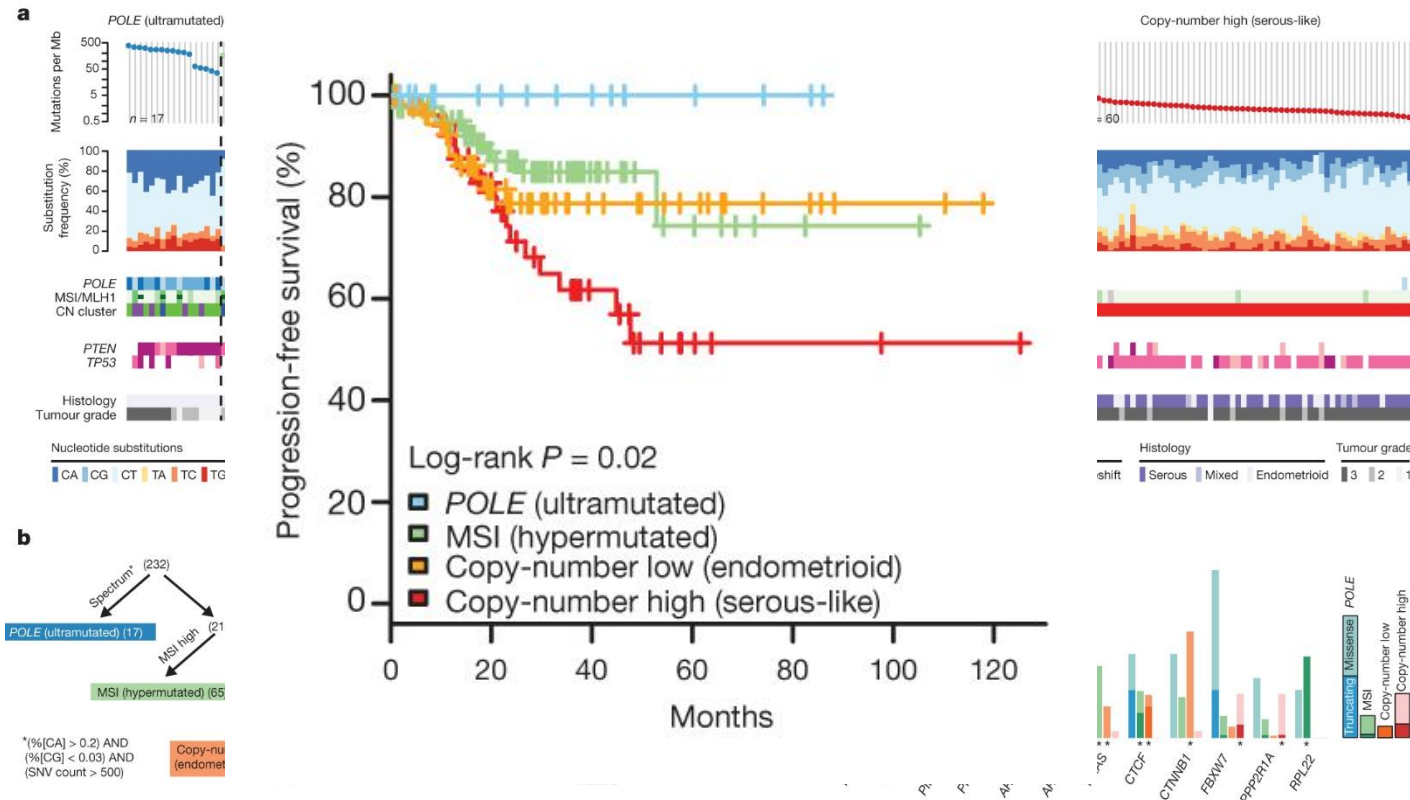
Endometrioid carcinoma,
FIGO grade 1



Histologically high-grade
endometrial carcinoma



POLE pathogenic
mutation



Cancer Genome Atlas (4 molecular groups)

❖ POLE (ultra-mutated)- Good

❖ MSI-H (hyper-mutated)

Nature. 2013; **497**: 67-73. ❖ Copy number low (NSMP)

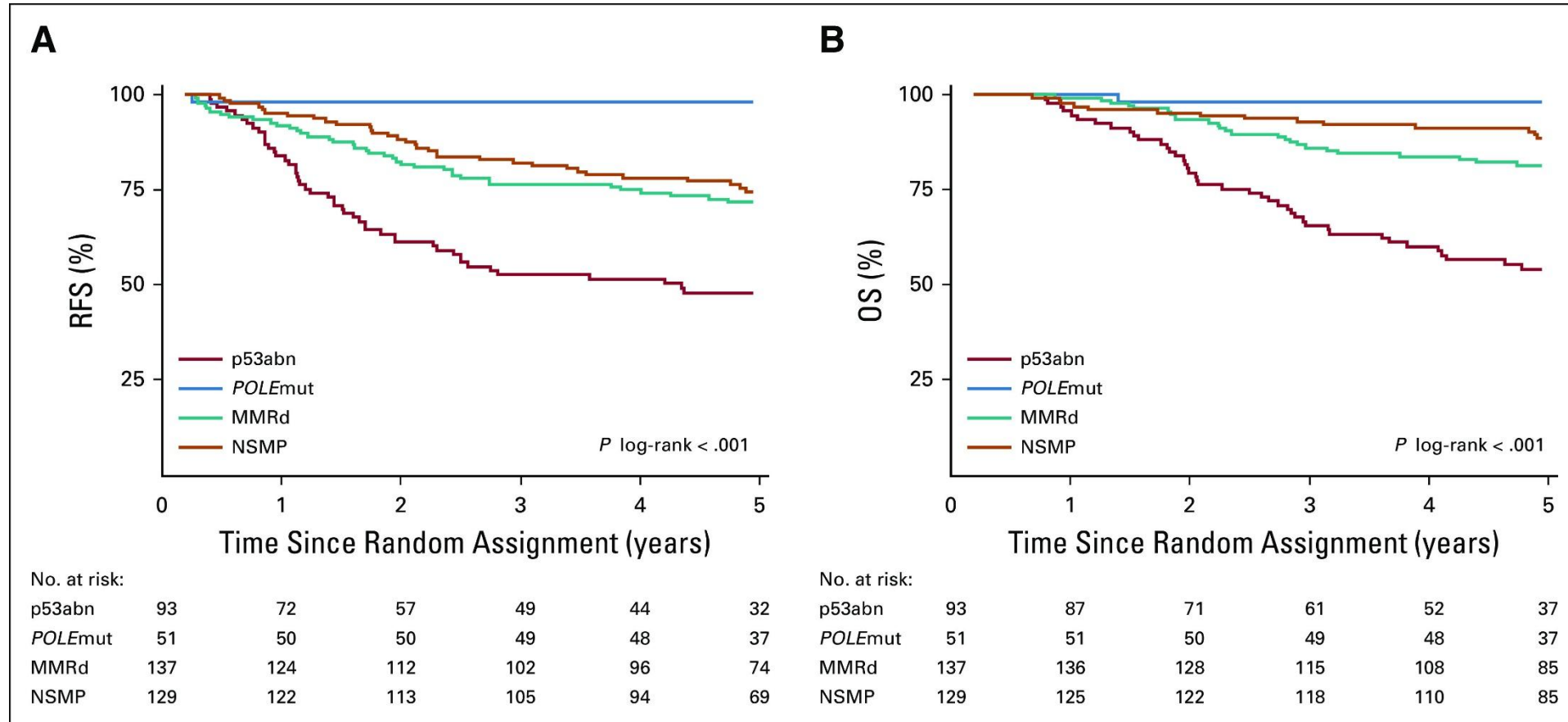
❖ Copy number high (serous-like) -Bad

PORTEC Clinical Trials

- PORTEC-1: 1990-1997, 714 patients: Pelvic EGRT better local control than no RT in intermediate to high-risk EC
- PORTEC-2: 2002-2006, 427 patients: VBT similar effect as EBRT in intermediate to high-risk EC
- PORTEC-3: 2006-2013, 686 patients: Chemoradiotherapy can significantly improve OS than RT alone in high-risk EC
- PORTEC-4A: Risk stratification according to molecular classification

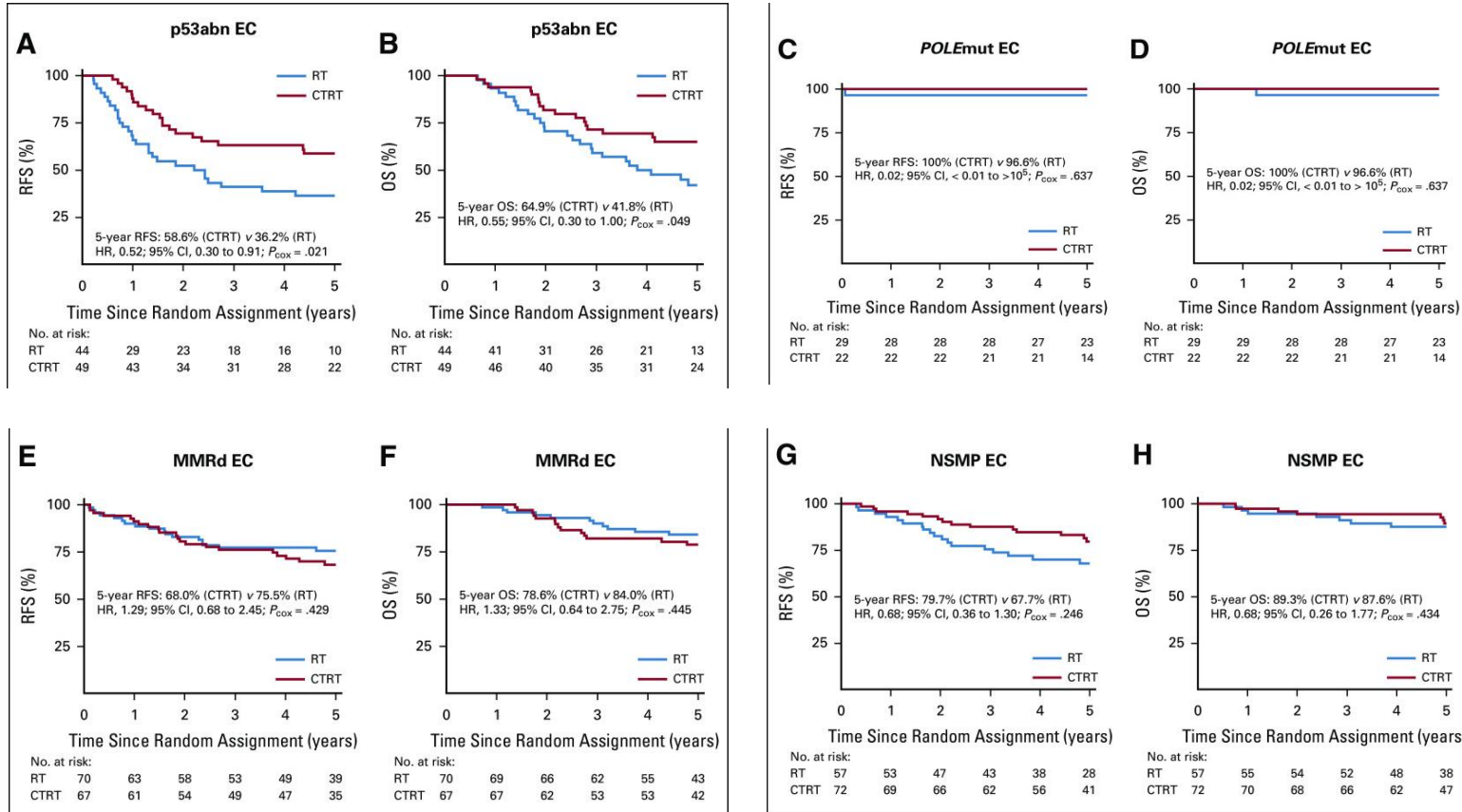
PORTEC 3 Clinical Trial

Prognostic significance of the TCGA groups



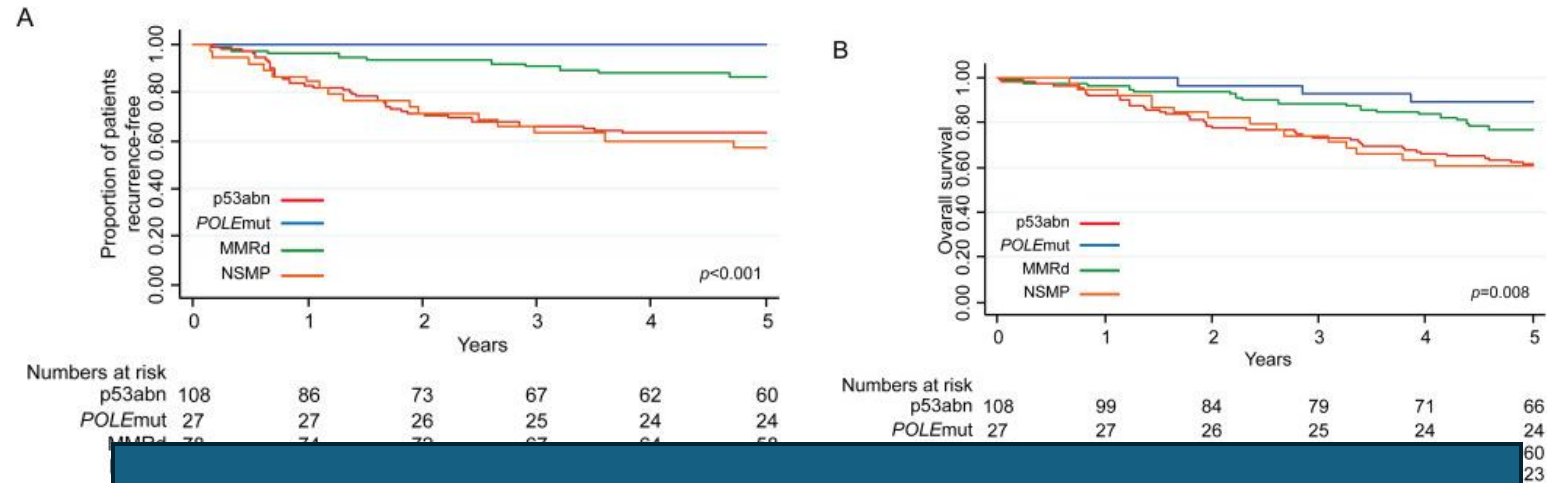
PORTEC 4A trial

Predictive potential of TCGA groups for adjuvant therapy

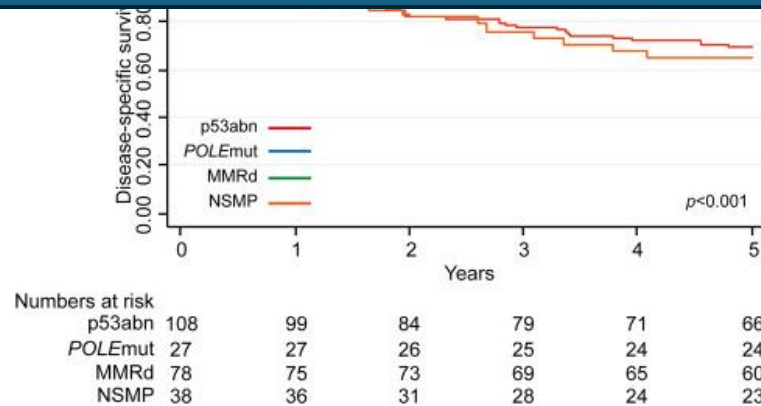


Danish Gynecologic Cancer Database

High grade EC not receiving adjuvant treatment



Patients with POLE mut have an excellent prognosis even with no adjuvant therapy



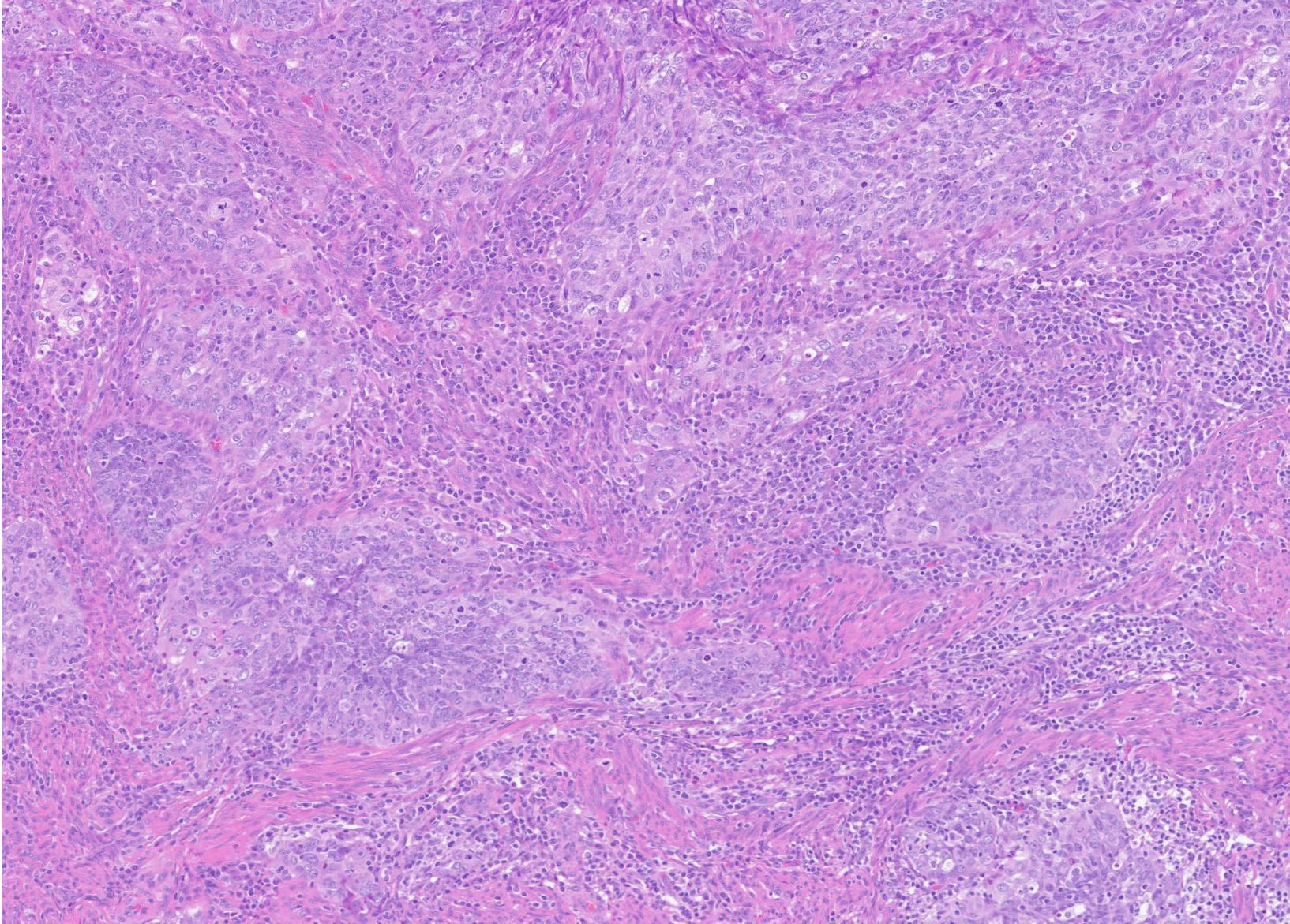
POLE mutated EC

- Gene encodes catalytic subunit of DNA polymerase epsilon
- Approximately 6-10% of the ECs
- EXCEPTIONALLY GOOD PROGNOSIS
- Treatment de-escalation: NO RT for low-stage; NO chemotherapy for high-stage??

POLE mutated EC (morphological hints)

- Some features can suggest POLE mutation:
 - Usually high tumor grade
 - Usually FIGO stage I
 - Tumor heterogeneity
 - Tumor infiltrating lymphocytes, Crohn's like response
 - Scattered tumor giant cells

Histopathology; 2018. 72(2): 248-258



POLE Testing in Clinical Practice

- NO Immunohistochemical surrogate
- NOT all variants are pathogenic
- Guidelines on interpretation only recently put forward
 - Sequencing of POLE “hotspots”: Exons 9,13,14 or Exons 9-14
 - Sanger vs. NGS: acceptable depend on access
 - Pathologists need to identify suitable tissue

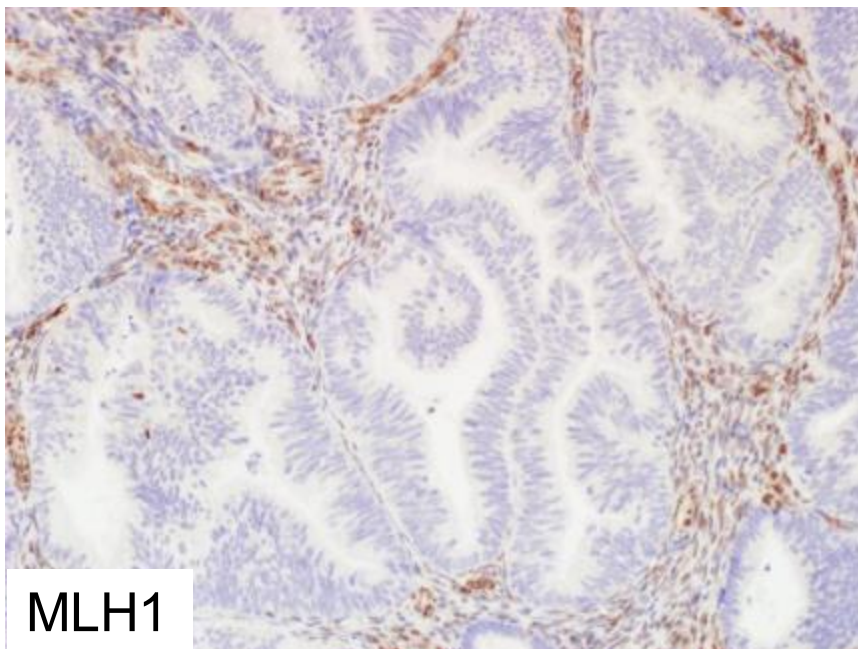
Only POLE Pathogenic Variants Matter

Protein change	Nucleotide Substitution
P286R	c. 857 C>G
V411L	c. 1231G>T/C
S297F	c. 890 C>T
S459F	c. 1376 C>T
A456P	c. 1366 G>C
F367S	c. 1100 T>C
L424I	c. 1270 C>A
M295R	c. 884 T>G
P436R	c. 1307 C>G
M444K	c. 1331 T>A
D368Y	c. 1102 G>T

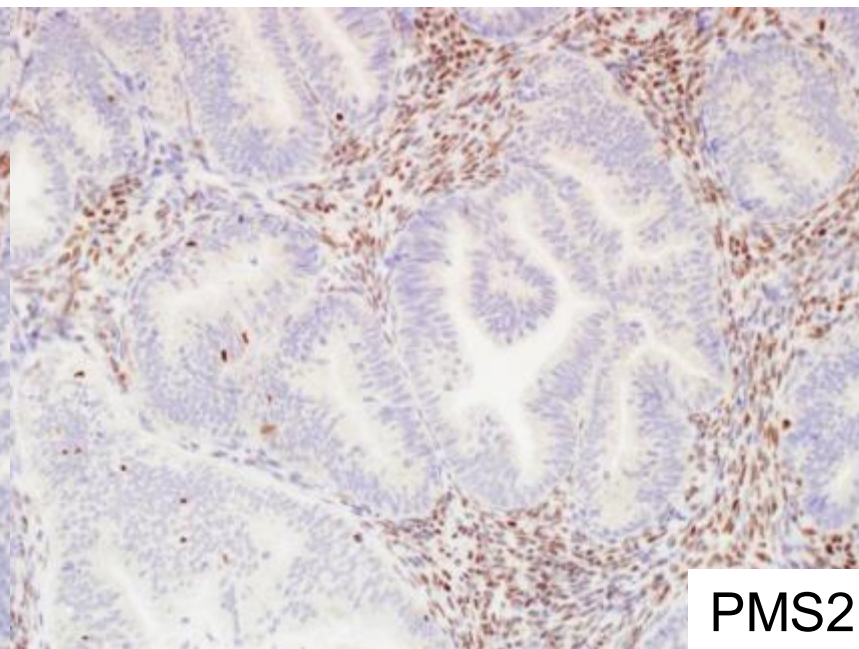
- EC with any of these 11 pathogenic variants is considered POLE mutated
- >80% of the POLE mutated ECs have the top 5 pathogenic variants (in bold)

Microsatellite Instability (dMMR) EC

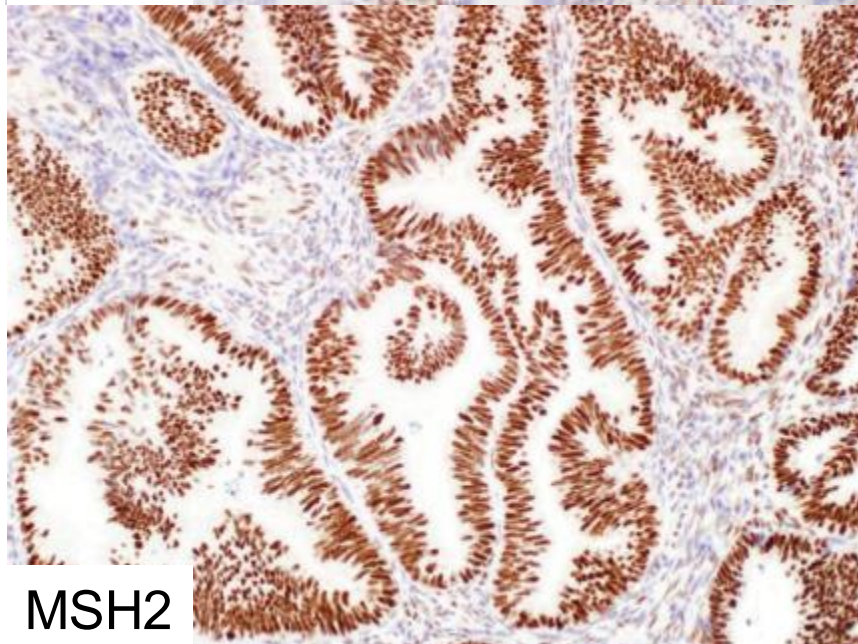
- Result of mismatch repair protein deficiency
- 25-30% of EC
- Majority sporadic; about 3% Lynch
- Usually TIL's and substantial LVSI
- Good response to RT. Chemotherapy does NOT improve prognosis.
 - Immune checkpoint therapy - **FDA approval for immunotherapy at high stage-respond better**



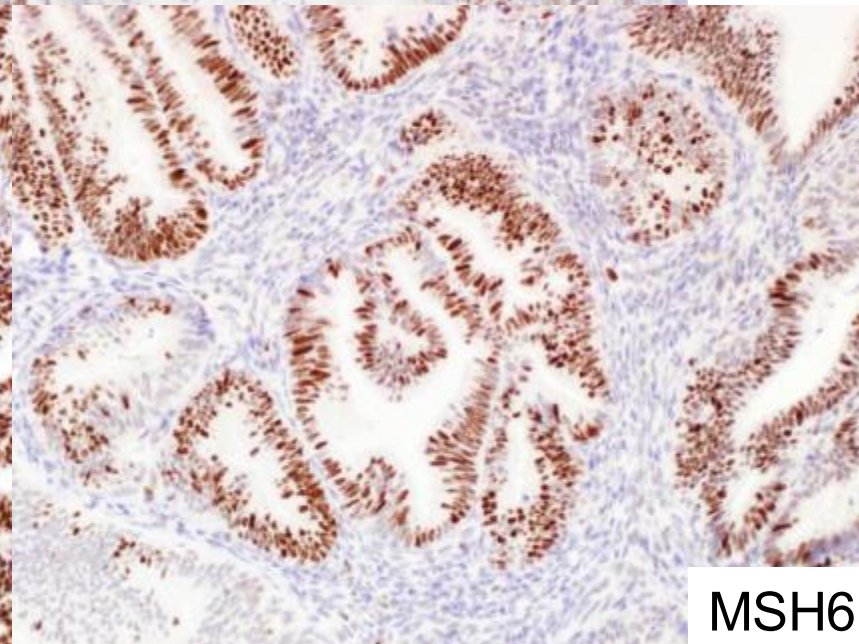
MLH1



PMS2



MSH2

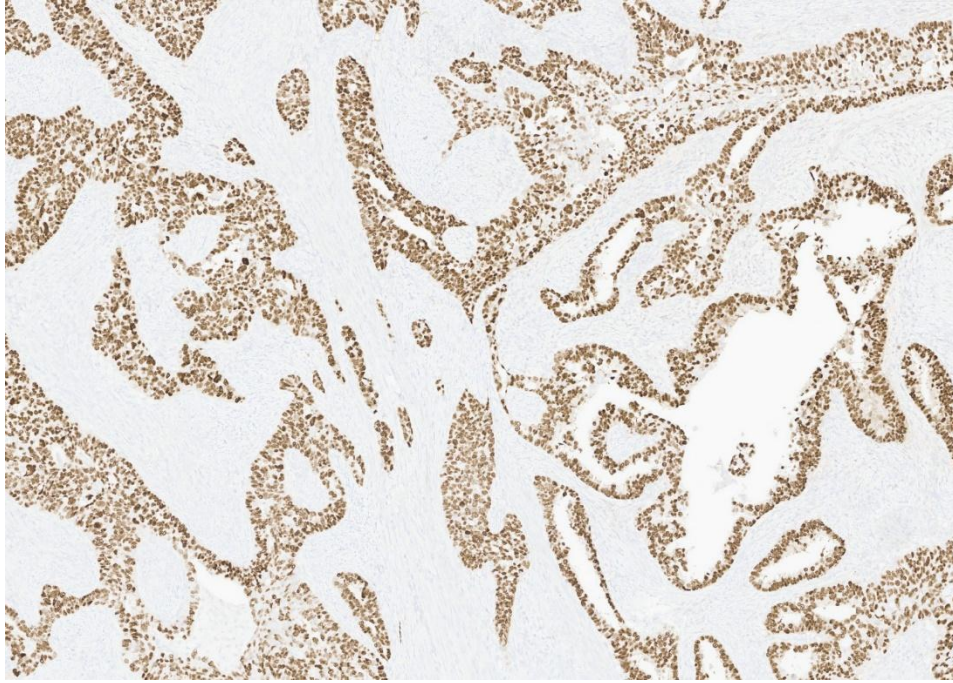


MSH6

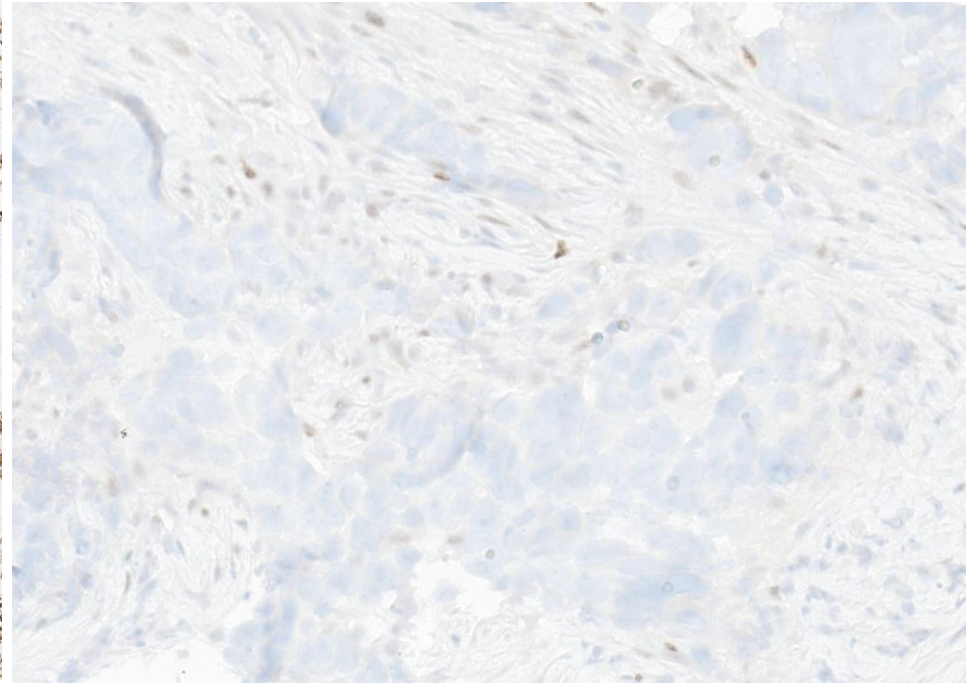
Copy number high (Serous-like) Group

- Typically TP53 mutated and need to exclude POLEmut and MMRd EC
- May show typical serous features or variant histology: high nuclear grade
- 15-20% OF EC
- Targeting HER2 are being used

P53 IHC mutated patterns

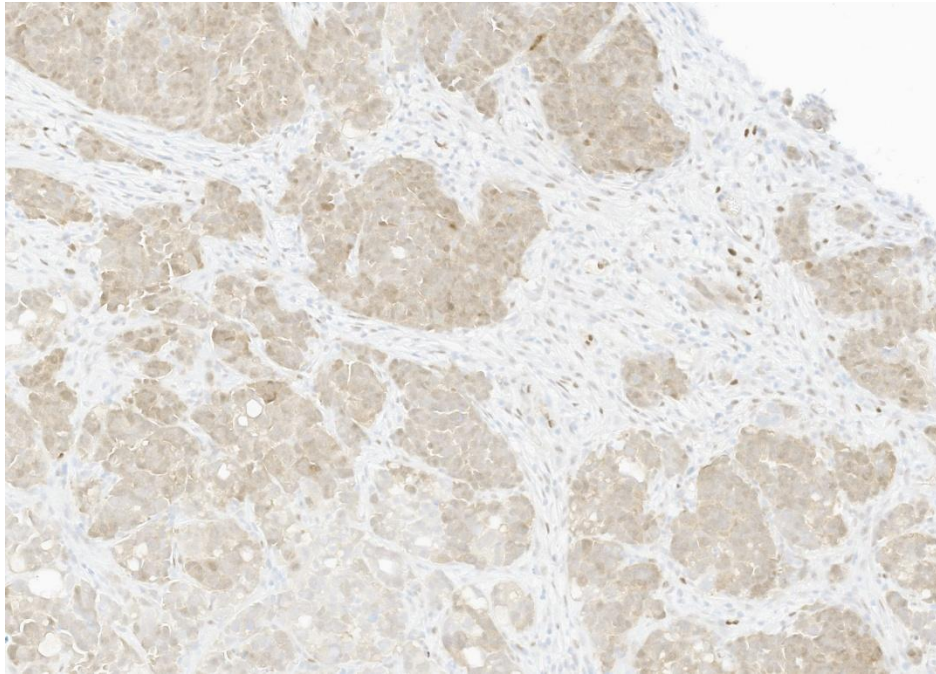


P53 nuclear overexpression

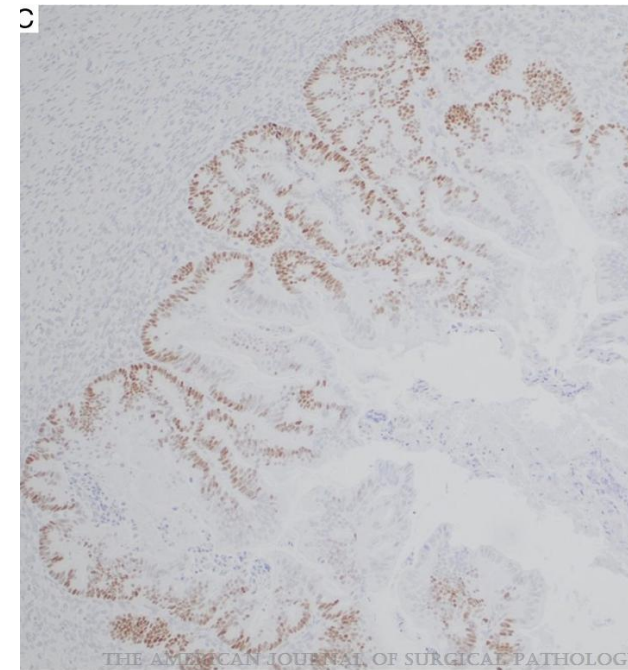


P53 loss (Null)

P53 IHC mutated patterns



P53 cytoplasmic pattern



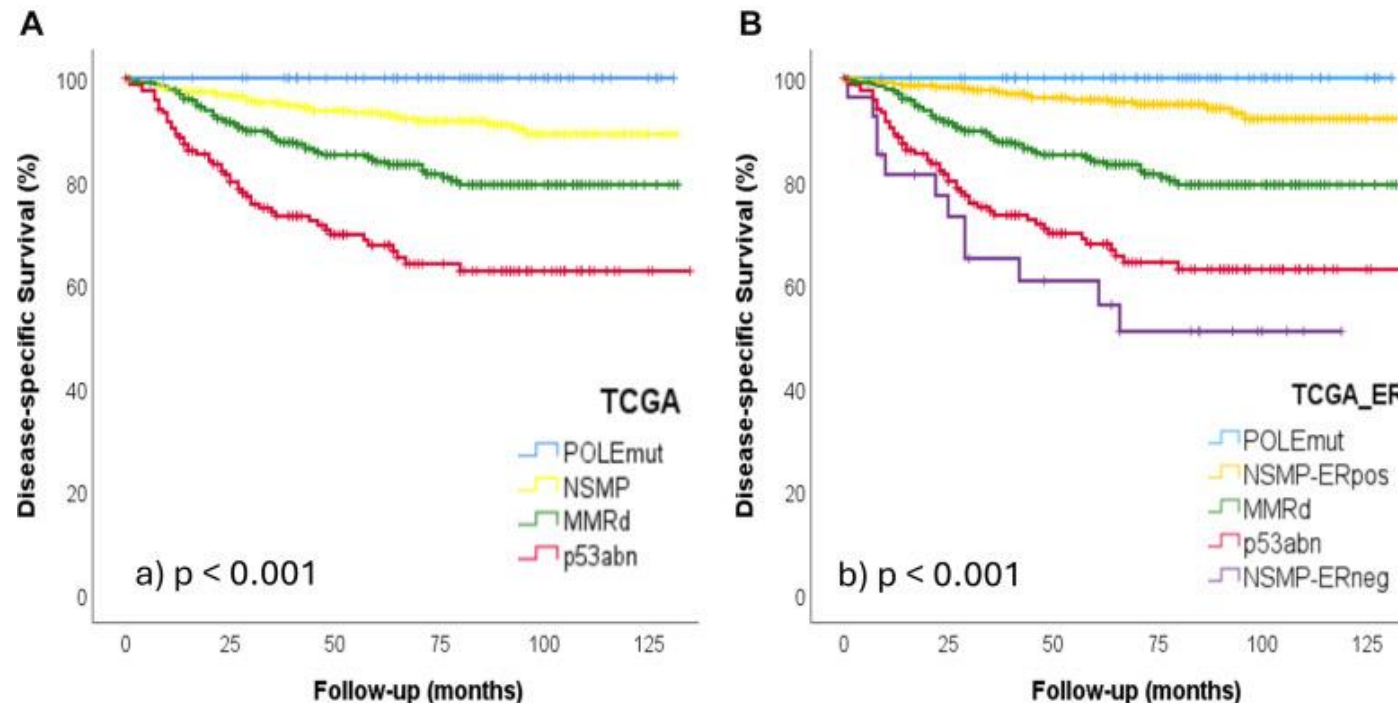
P53 terminal differentiation
pattern

P53 IHC and molecular correlation is around 92-95%

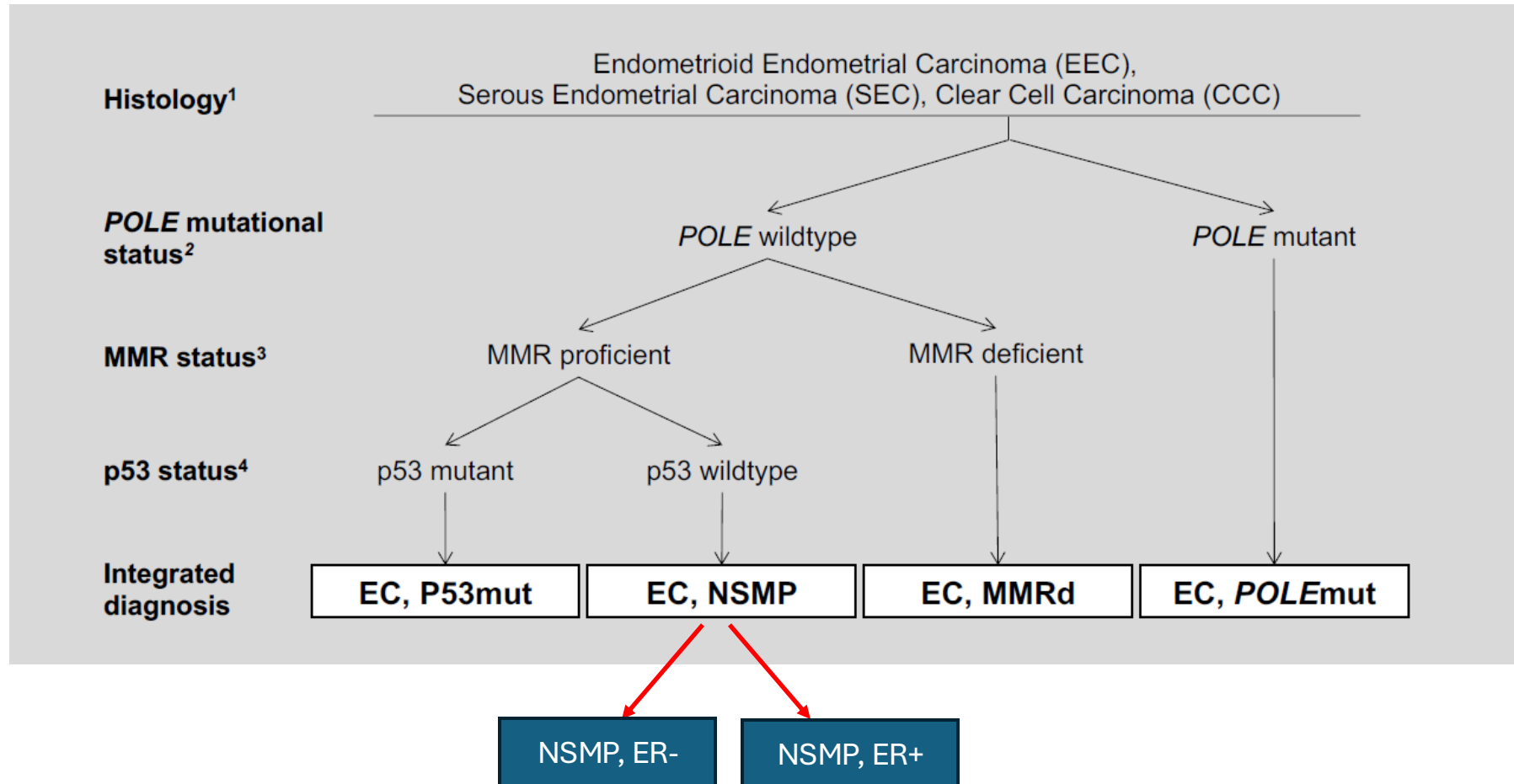
Am J Surg Path; 2025 March 11

Copy Number Low Group (NSMP)

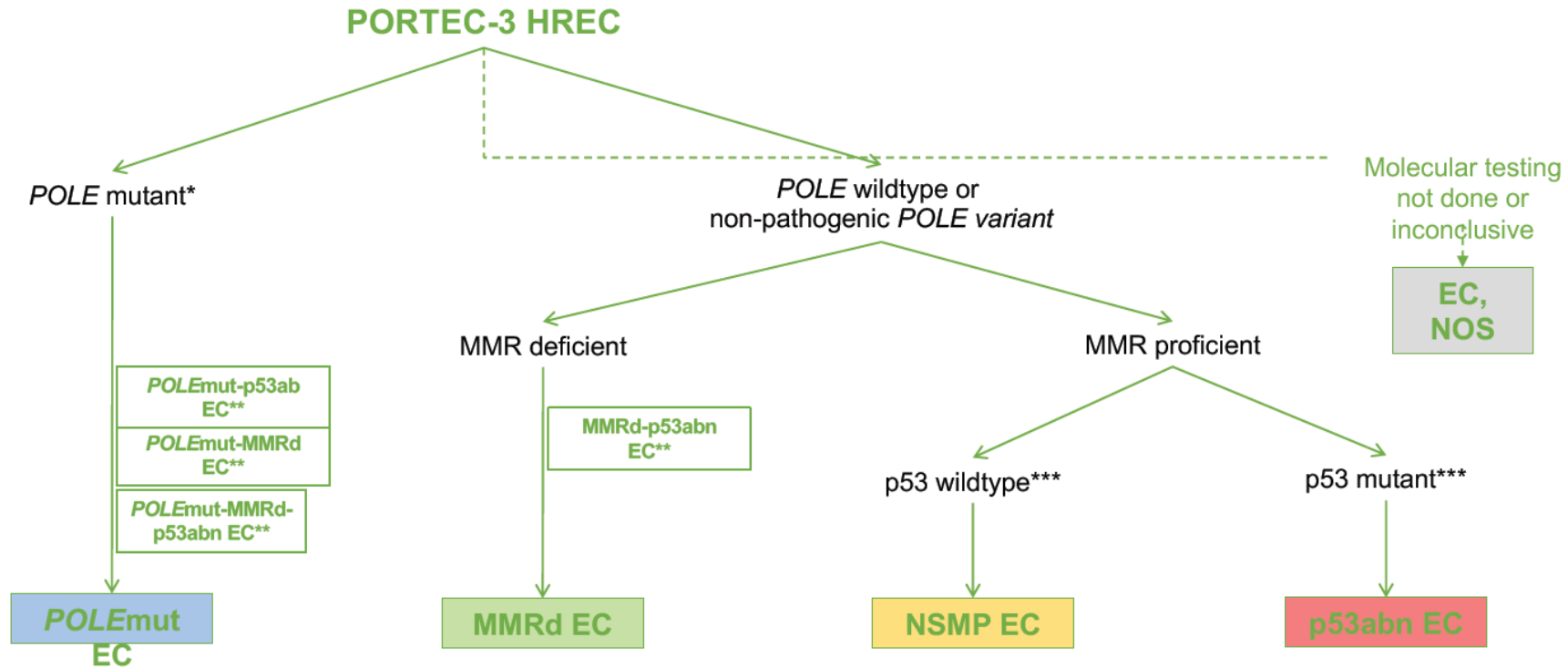
- “No specific molecular profile”
- 48-52% of EC (heterogeneous)
- It is NOT a “waste basket” group



The integrated histology-molecular classification Scheme



Multiple molecular classifiers



Adapted from Vermij et al, *Histopathology* 2020

*Pathogenic *POLE* exonuclease domain mutations (EDM) as per León-Castillo et al, *J Pathol* 2019

**León-Castillo et al, *J Pathol* 2019

***p53 IHC is as a excellent surrogate marker for mutational status (Singh et al, *J Pathol* 2019)

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SPECIAL ARTICLE



FIGO staging of endometrial cancer: 2023

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Abstract

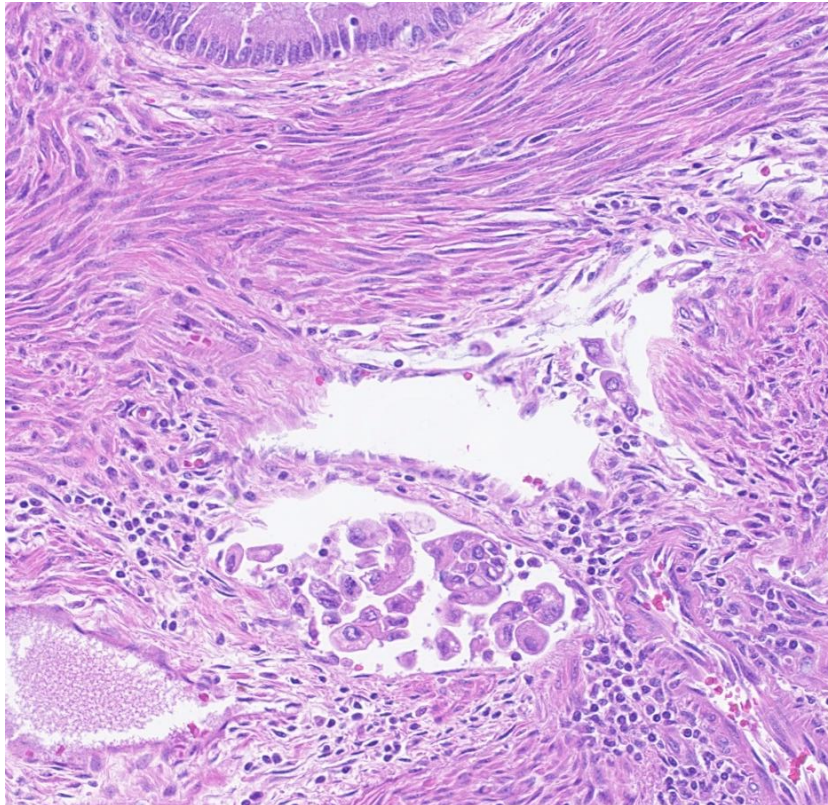
Introduction: Many advances in the understanding of the pathologic and molecular features of endometrial cancer have occurred since the FIGO staging was last updated in 2009. Substantially more outcome and biological behavior data are now available regarding the several histological types. Molecular and genetic findings have accelerated since the publication of The Cancer Genome Atlas (TCGA) data and provide improved clarity on the diverse biological nature of this collection of endometrial cancers and their differing prognostic outcomes. The goals of the new staging system are to better define these prognostic groups and create substages that indicate more appropriate surgical, radiation, and systemic therapies.

Methods: The FIGO Women's Cancer Committee appointed a Subcommittee on Endometrial Cancer Staging in October 2021, represented by the authors. Since then, the committee members have met frequently and reviewed new and established evidence on the treatment, prognosis, and survival of endometrial cancer. Based on these data, opportunities for improvements in the categorization and stratification of these factors were identified in each of the four stages. Data and analyses from the molecular and histological classifications performed and published in the recently developed ESGO/ESTRO/ESP guidelines were used as a template for adding the new subclassifications to the proposed molecular and histological staging system.

Results: Based on the existing evidence, the substages were defined as follows:

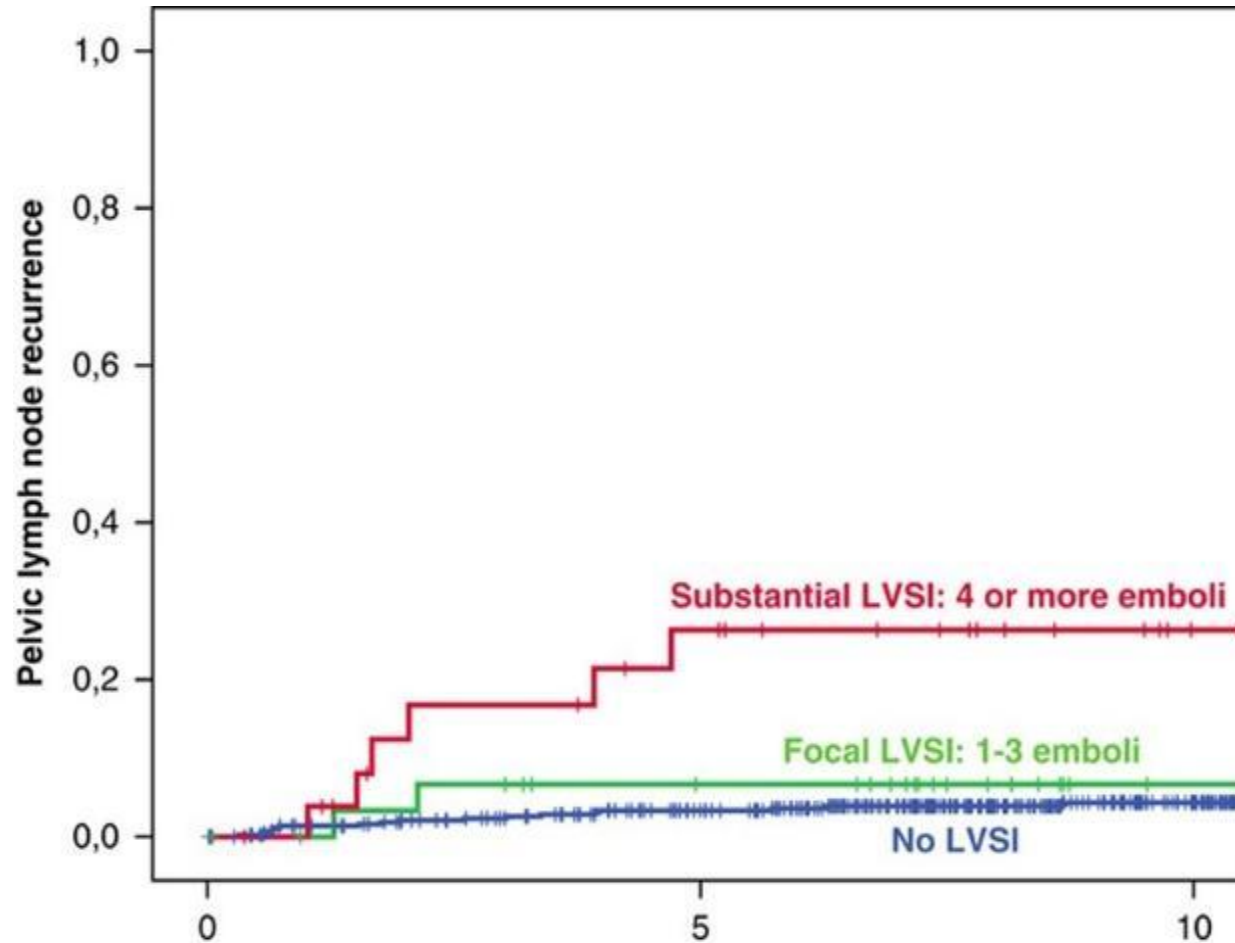
Stage I (IA1): non-aggressive histological type of endometrial carcinoma limited to a polyp or confined to the endometrium; (IA2) non-aggressive histological types of endometrium involving less than 50% of the myometrium with no or focal lymphovascular space invasion (LVSI) as defined by WHO criteria; (IA3) low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement; (IB) non-aggressive histological types involving 50% or more of the myometrium with no LVSI or focal LVSI; (IC) aggressive histological types, i.e. serous,

I. Major change of 2023 FIGO stage-LVSI



- Substantial LVSI for non-aggressive histological types are IIB
- No or focal LVSI for non-aggressive histological types are the followings:
 - IA1: no invasion
 - IA2: <1/2 invasion
 - IB: >1/2 invasion

Substantial LVSI: ≥ 4 LVS on one given H&E slide?



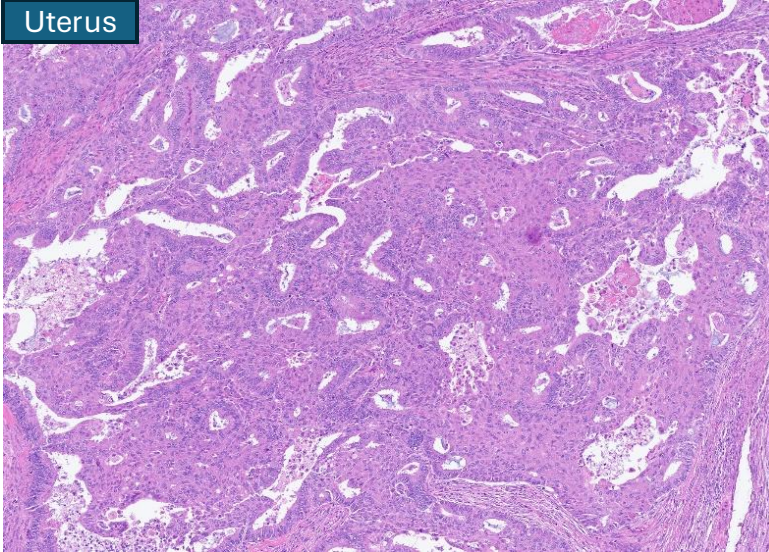
International Journal of Gynecological Pathology
41:220-226, Lippincott Williams & Wilkins, Baltimore
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Original Article

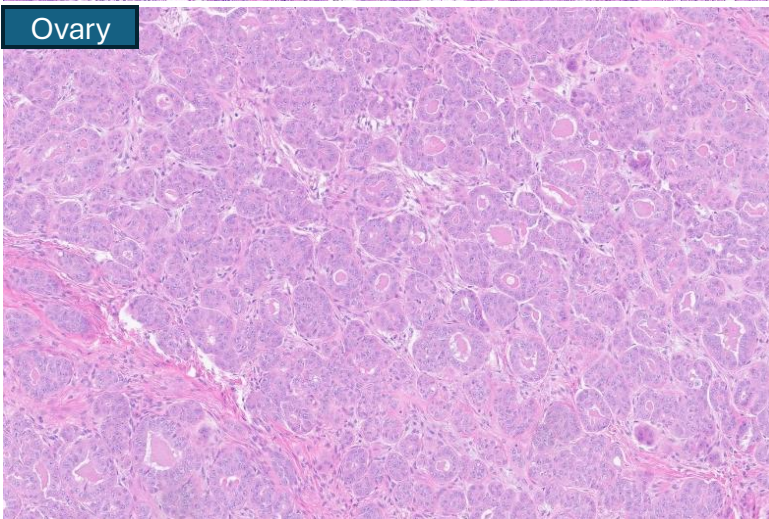
Defining Substantial Lymphovascular Space Invasion in Endometrial Cancer

Elke E.M. Peters, M.D., Alicia León-Castillo, M.D., Vincent T.H.B.M. Smit, M.D., Ph.D.,
Marie Boennelycke, M.D., Estrid Hogdall, Ph.D., Claus Hogdall, M.D., Ph.D.,
Carlen Creutzberg, M.D., Ph.D., Ina M. Jürgenliemk-Schulz, Ph.D., Jan J. Jobsen, M.D., Ph.D.,
Jan Willem M. Mens, M.D., Ludy C.H.W. Lutgens, M.D.,
Elzbieta M. van der Steen-Banasik, M.D., Gitte Ortoft, M.D., Ph.D.,
Tjalling Bosse, M.D., Ph.D., and Remi Nout, M.D., Ph.D.

Uterus



Ovary

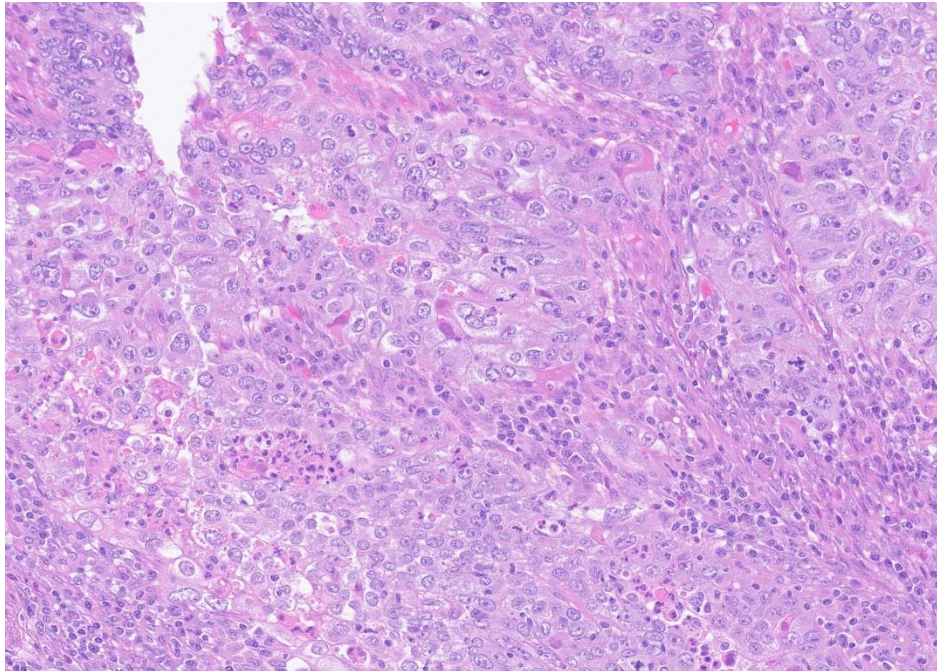


Synchronous EM and Ovarian carcinomas

- No >50% myometrial invasion
- No substantial LVSI
- No additional metastasis
- Ovarian tumor is unilateral, no capsular invasion or rupture (pT1a)

Low-grade endometrioid limited to uterus and ovary – IA3

III. Major change and controversy of the 2023 FIGO stage Incorporate MC to certain EC



- Aggressive histological types limited to a polyp or no myometrial invasion: IC
- Aggressive histological types with any myometrial invasion: IIC

What about incorporate MC into the EC?

FIGO EC stages with molecular classification

- Stage designation after Molecular findings in patients with endometrial cancers
 - Stage IAmPOLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
 - Stage IICmp53abn p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type
-
- The Final 2023 FIGO stage will be changed/updated according to the molecular findings, usually 2-3 weeks after the initial stage was assigned

Gross Hysterectomy-New Practice

- Taking more sections of the endometrial tumor (routinely 5mm per section)
- Submit the entire ovaries and fallopian tubes with any of the following risk factors:
 - High grade tumor
 - Deep invasive tumor
 - Synchronous tumors



EM CA Molecular Testing Work Flow-09/23



Hysterectomy (all in house cases)



All endometrial carcinomas regardless of histologic types or stages-
Prelim FIGO (2023) stage issued
Comment of "APEMREX" added



Mayo GYN EM ca panel (MCECP)



Addendum or amendment issued to report the final MMR,
p53, POLE mutation status and final molecular stage
(APMCECP)

Why on hysterectomy not on biopsy?

- Considering our own institutional practice
 - Sentinel LN
 - Routine IHC for ER, PR, p53, and MMR
 - Turn around time
- The cost of the molecular panel
 - Single gene (POLE) was not available
 - The panel is relatively inexpensive
- Sampling issue

Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment



Aline Talhouk^{a,1}, Lien N. Hoang^{b,c,1}, Melissa K. McConechy^{a,d}, Quentin Nakonechny^b, Joyce Leo^b, Angela Cheng^e, Samuel Leung^e, Winnie Yang^a, Amy Lum^a, Martin Köbel^f, Cheng-Han Lee^g, Robert A. Soslow^c, David G. Huntsman^a, C. Blake Gilks^{b,2}, Jessica N. McAlpine^{h,*,2}

^a Department of Pathology and Laboratory Medicine, University of British Columbia and BC Cancer Agency, Vancouver, British Columbia, Canada

^b Department of Pathology and Laboratory Medicine, University of British Columbia and Vancouver General Hospital, Vancouver, British Columbia, Canada

^c Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

Table 3

Discordant cases according to ProMisE subclassification.

Case	Specimen	Pathology	MMR IHC	POLE	p53	Initial Assignment Reassessment		Final ProMisE	Retest
1	Diagnostic	CAH + gr 1 EM	intact	no mut	abn	p53 abn	Retest: No POLE mut found	p53 abn	Discordant
	Hysterectomy	gr 1 EM, stage IB	intact	P286S*	abn	POLE EDM	Retest validates	POLE EDM	
2	Diagnostic	gr 2 EM	MSH6 loss	no mut	wt	MMR-D	Retest: Δ to intact	p53 wt	Concordant
	Hysterectomy	gr 2 EM, stage IB	intact	no mut	wt	p53 wt	Retest: confirms intact	p53 wt	
3	Diagnostic	gr 1 EM	MSH2/MSH6 loss	no mut	wt	MMR-D	Retest: changed to intact	p53 wt	Concordant
	Hysterectomy	gr 2 EM, stage IA	intact	no mut	wt	p53 wt	Retest confirms intact	p53 wt	
4	Diagnostic	gr 3 undiff	MSH2/MSH6 loss	P441L	abn	MMR-D	Retest confirms MSH2/MSH6 loss	MMR-D	Concordant
	Hysterectomy	gr 3 SC, stage IB	intact	P441L	abn	POLE EDM	Retest: Δ to MSH2/MSH6 loss	MMR-D	
5	Diagnostic	gr 1 EM	intact	no mut	wt	p53 wt	Retest confirms intact	p53 wt	Discordant
	Hysterectomy	gr 3 EM, stage IB	MLH1/PMS2 loss	no mut	wt	MMR-D	Retest confirms loss of MLH1	MMR-D	
6	Diagnostic	gr 1 EM	intact	P286R	wt	POLE EDM	Retest validates	POLE EDM	Discordant
	Hysterectomy	gr 1 EM, stage IA	intact	no mut	wt	p53 wt	Retest: No POLE mut found	p53 wt	

The Mayo MCECP Panel



1-800-533-1710

MayoComplete Endometrial Panel

MCECP

PATIENT NAME [REDACTED]				ORDER NUMBER [REDACTED]
PATIENT ID [REDACTED]	DATE OF BIRTH [REDACTED]	AGE [REDACTED]	SEX Female	REQUESTED BY LONGWEN CHEN
COLLECTED 8/7/2023, 3:20 PM	RECEIVED 8/14/2023, 1:06 PM	REPORTED 8/27/2023, 1:43 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location.				
PXMHMAINOR ARZ PXMH MAIN OR Phoenix AZ 85054				

The MCECP panel includes the following 19 genes: ATM, ATR, BRCA1, BRCA2, CDK12, **CTNNB1**, EPCAM, ERRBB2, FEXW7, **L1CAM**, MLH1, MSH2, MSH6, NBN, PALB2, **PMS2**, **POLE**, PP2R1A, and **TP53**

What's wrong with this MC report?

RESULT

The results provided within this report represent molecular testing results only. Please refer to the Surgical Pathology report for the integrated molecular and pathology diagnosis (if applicable).

Provided diagnosis: endometrial carcinoma

Microsatellite Instability (MSI) status: High (MSI-H)

The following ALTERATIONS (clinically relevant variants and variants of unknown significance) were detected:

Gene: POLE
DNA Change: c.3587C>T (Exon 30)
Amino Acid Change: p.T1196M (Thr1196Met)
Variant Allele Frequency: 33.2%

Gene: POLE
DNA Change: c.2554C>T (Exon 22)
Amino Acid Change: p.Q852* (Gln852*)
Variant Allele Frequency: 6.8%

Gene: MSH6
DNA Change: c.2177T>C (Exon 4)
Amino Acid Change: p.F726S (Phe726Ser)
Variant Allele Frequency: 7.5%

Gene: MSH6
DNA Change: c.3261del (Exon 5)
Amino Acid Change: p.F1088Sfs*2 (Phe1088Serfs*2)
Variant Allele Frequency: 8.2%

Gene: MSH6
DNA Change: c.3261dup (Exon 5)
Amino Acid Change: p.F1088Lfs*5 (Phe1088Leufs*5)
Variant Allele Frequency: 33%

Gene: MSH6
DNA Change: c.2332_2335dup (Exon 4)

What happened after 2 years?

- Problem #1
 - For stages III or IV EC, one patient is allowed one molecular panel per year!
- Problem #2
 - The MC panel sometimes takes longer than 2 weeks- miss the treatment window for adjuvant therapy
- A big question raised
 - Do we really need MC for low-grade low stage ER/PR+, p53 wild type, and MMR proficient ECs?

EM CA Molecular Classification Work Flow- Current



Hysterectomy (all in house cases)

All endometrial carcinomas regardless of histologic type-Pathology report on histology Dx, IHC of ER, PR, p53, MMR, and Prelim FIGO (2023) Stage I and II

All endometrial carcinomas regardless of histologic type-Pathology report on histology Dx, IHC of ER, PR, p53, MMR, and Prelim FIGO (2023) Stage III or IV

Mayo GYN EM ca panel (MCECP)

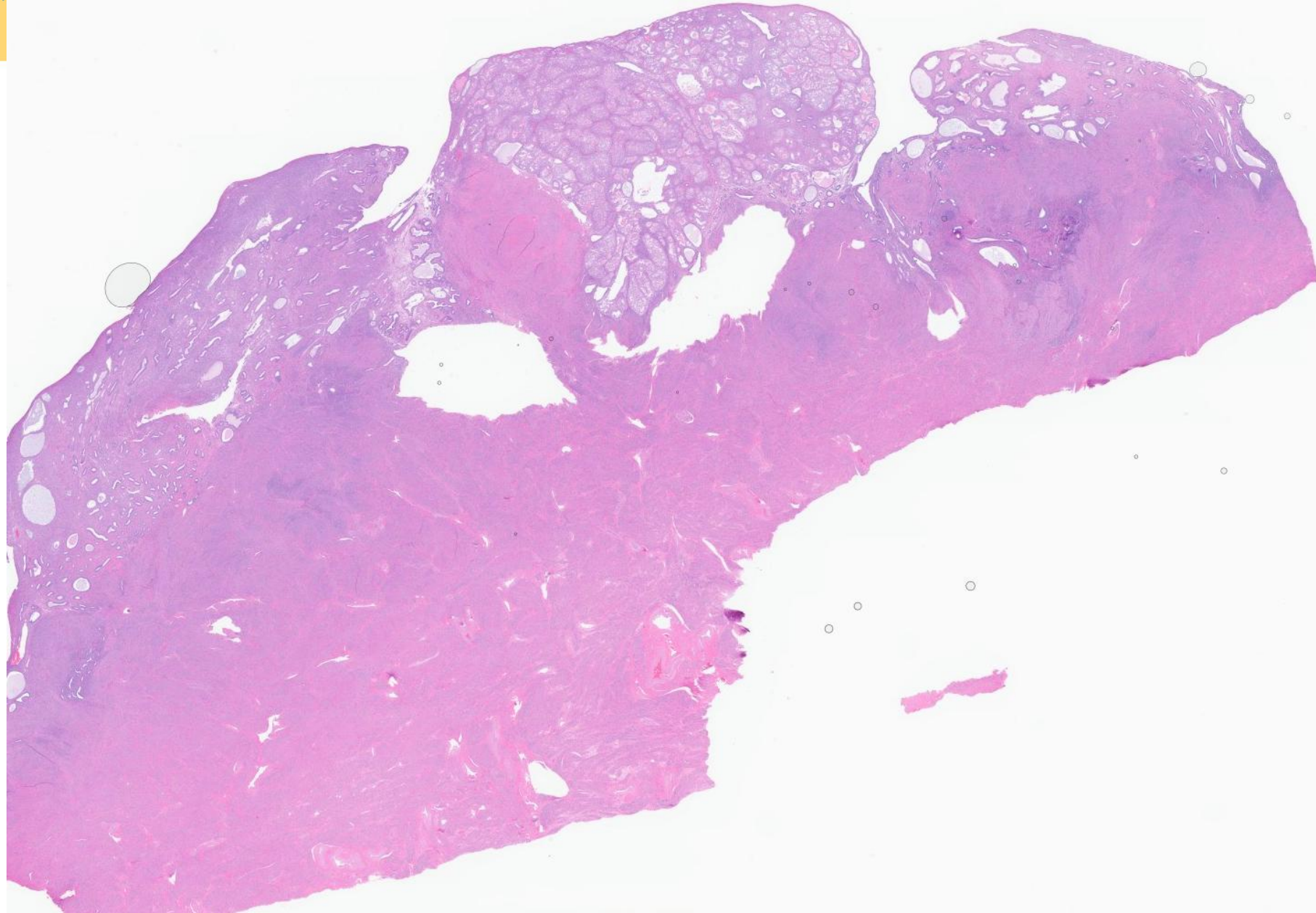
Caris GYN Molecular Panel

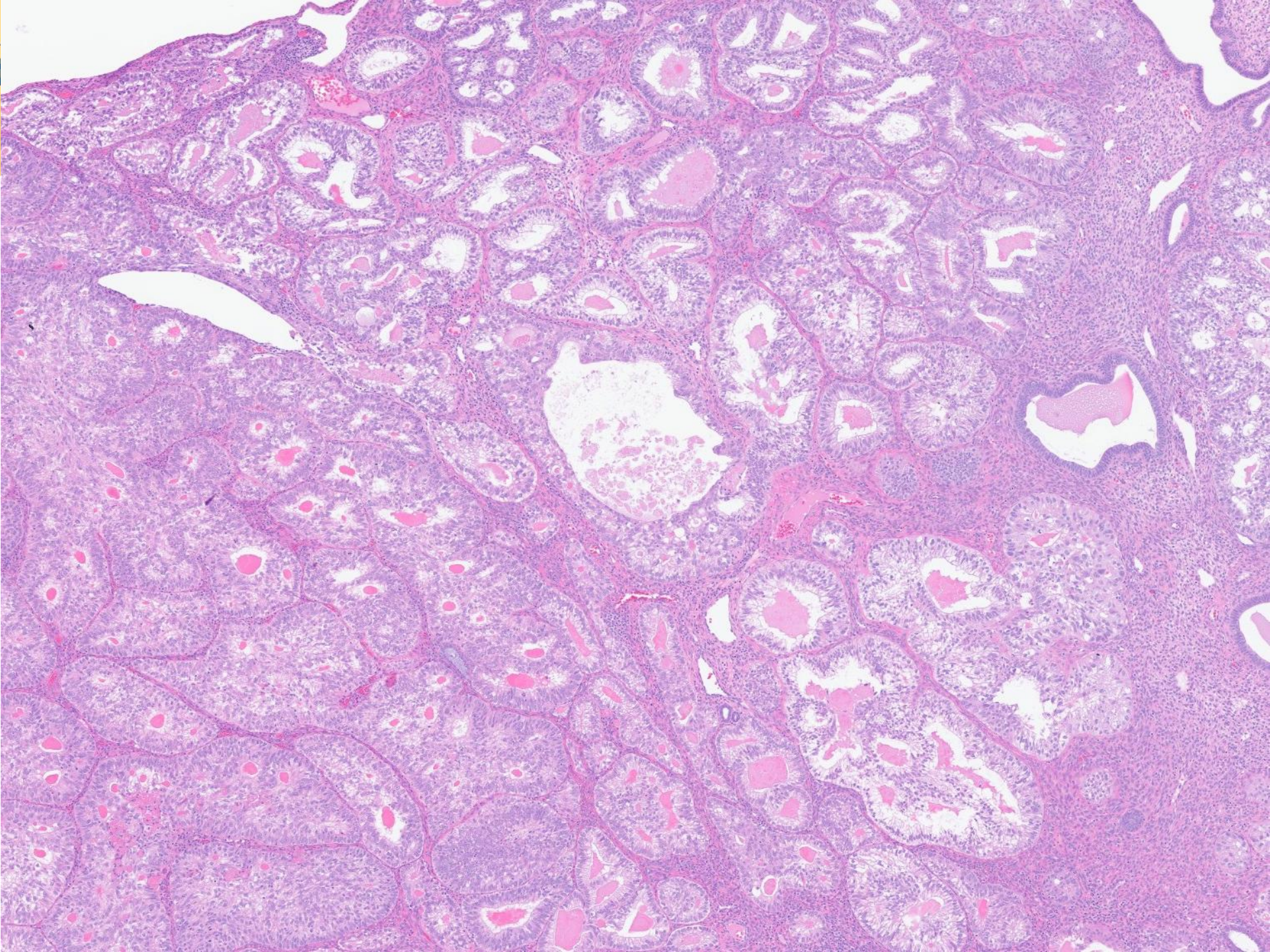
Addendum or amendment issued to report the final MMR, p53, POLE mutation status and final molecular stage

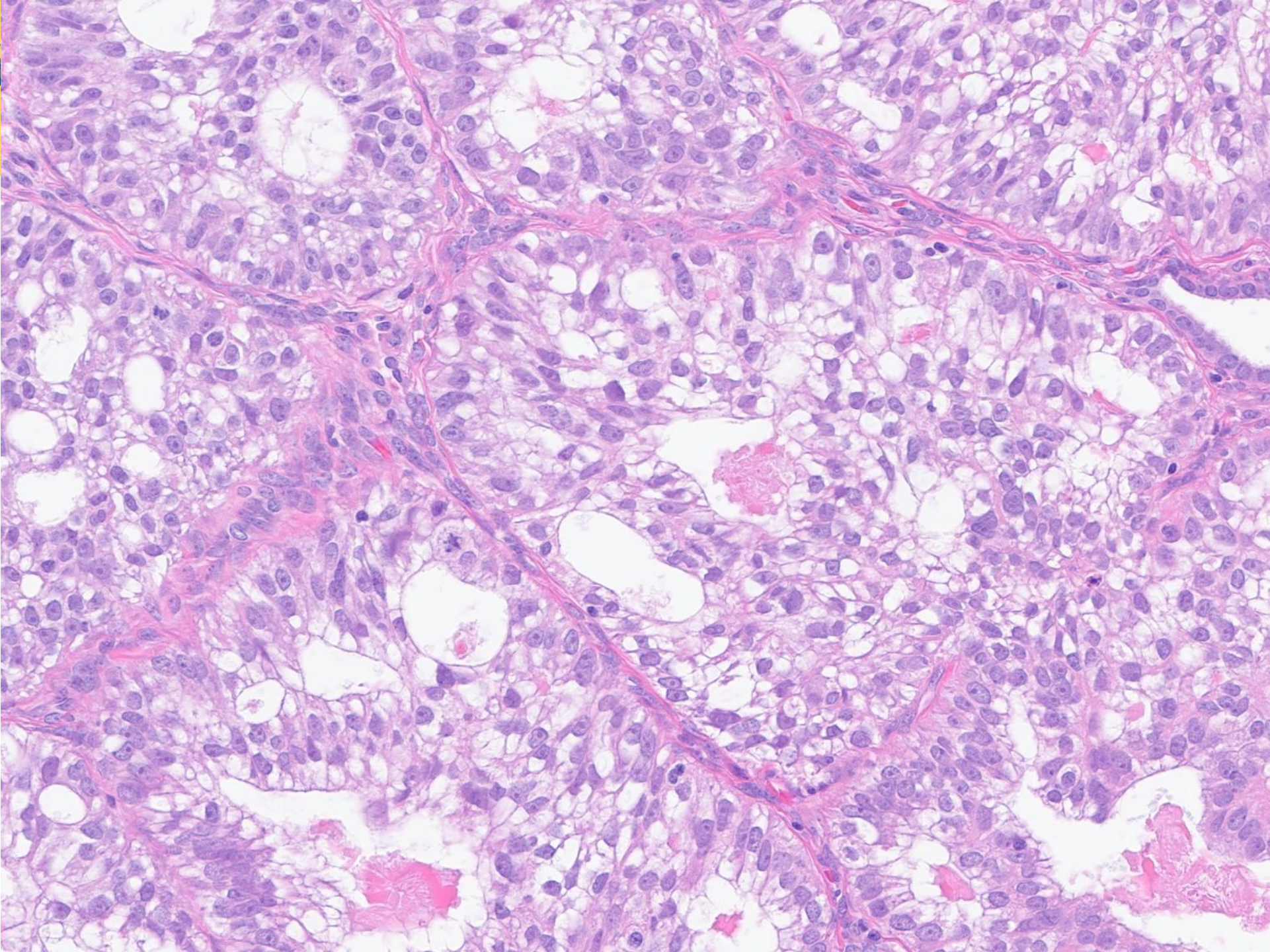
Addendum or amendment issued to report the final MMR, p53, POLE mutation status and final molecular stage

Case 1

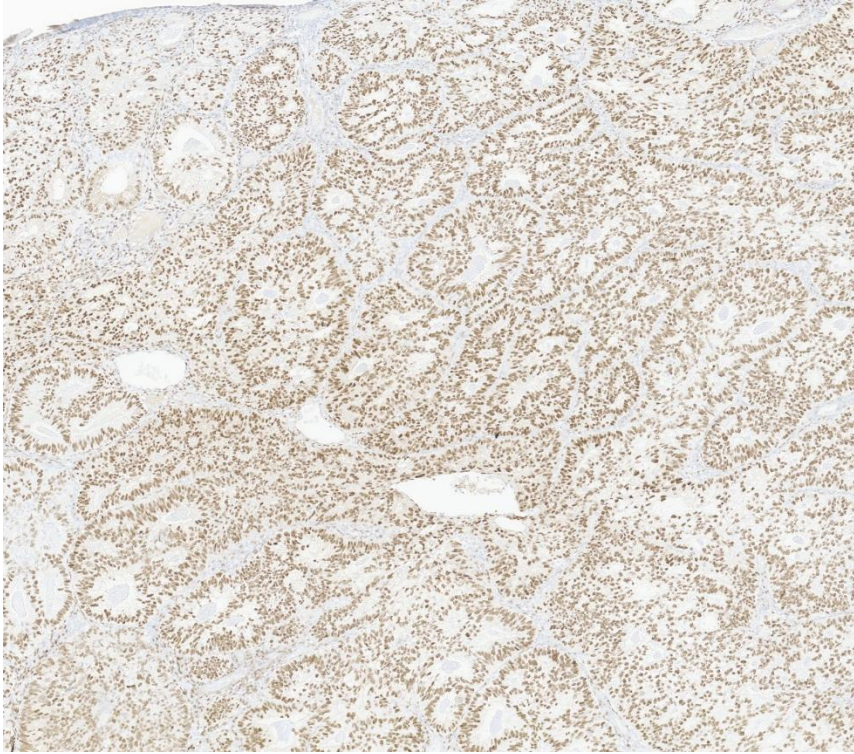
- A 62-year-old patient with post-menopausal bleeding
- Endometrial biopsy performed at the outside institution reported as FIGO grade 2 endometrioid carcinoma.
- A hysterectomy was performed, frozen section confirmed carcinoma, SLN was also performed



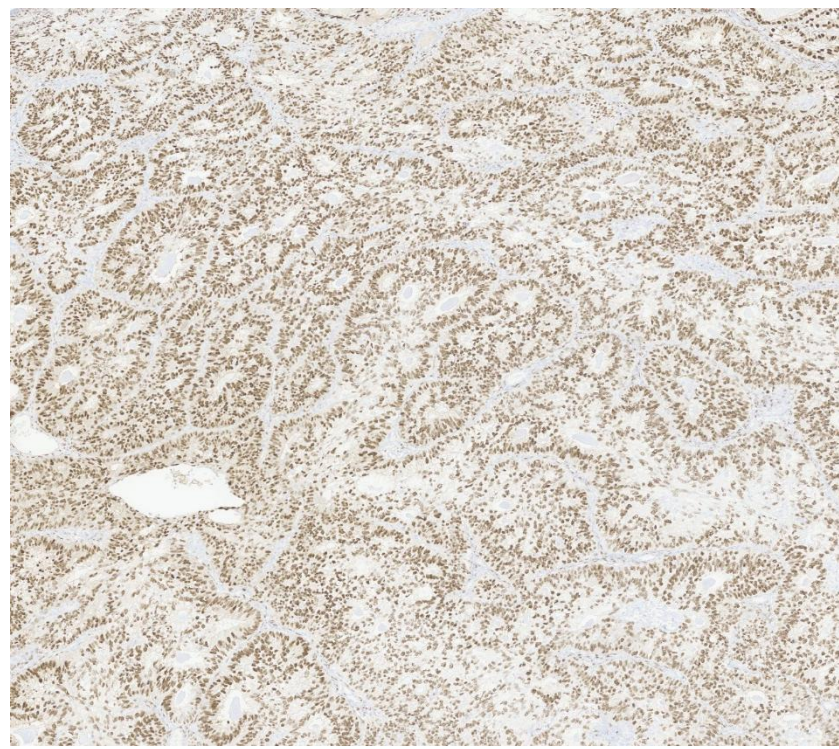




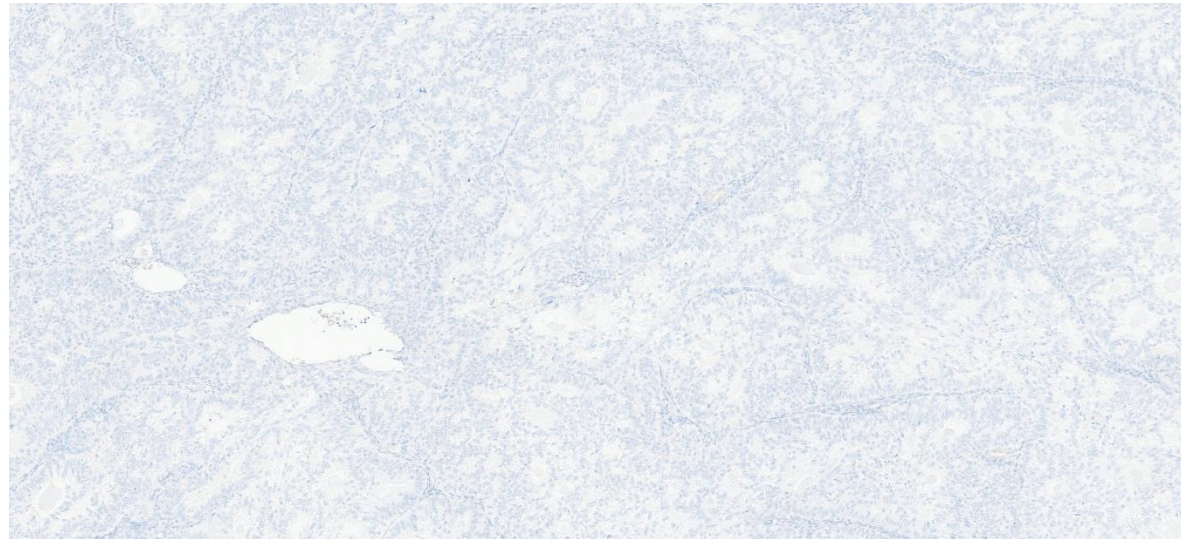
ER



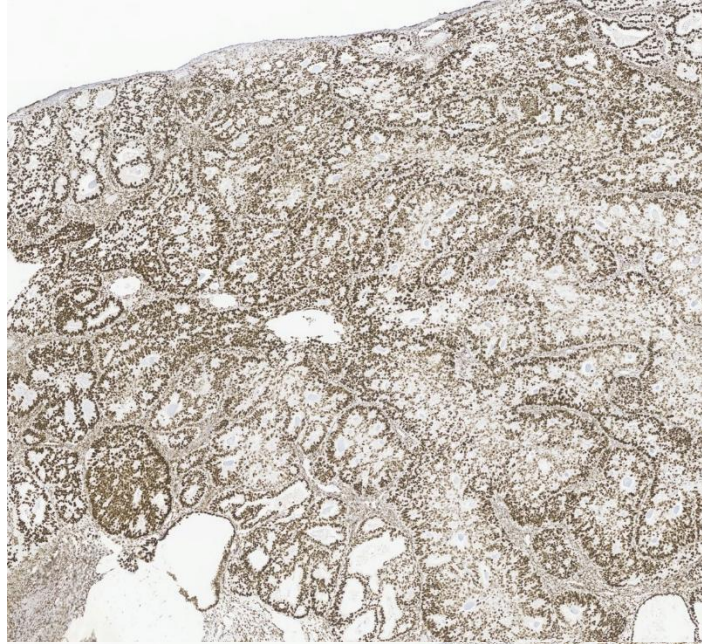
PR



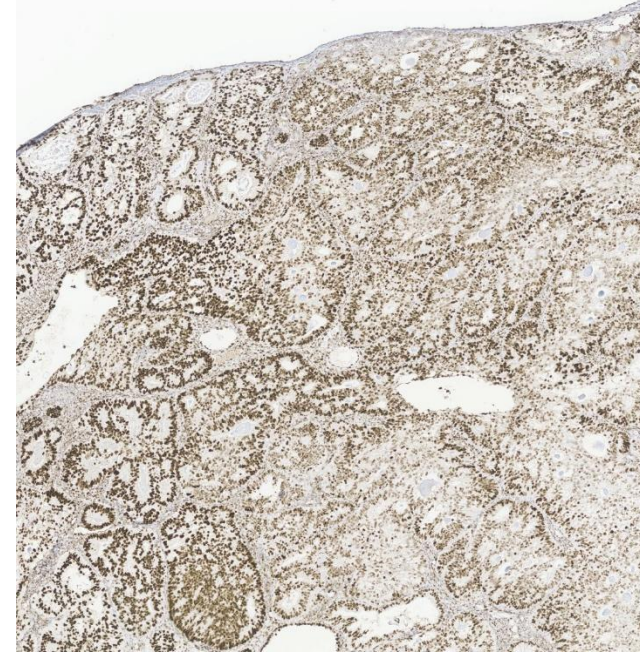
Napsin A



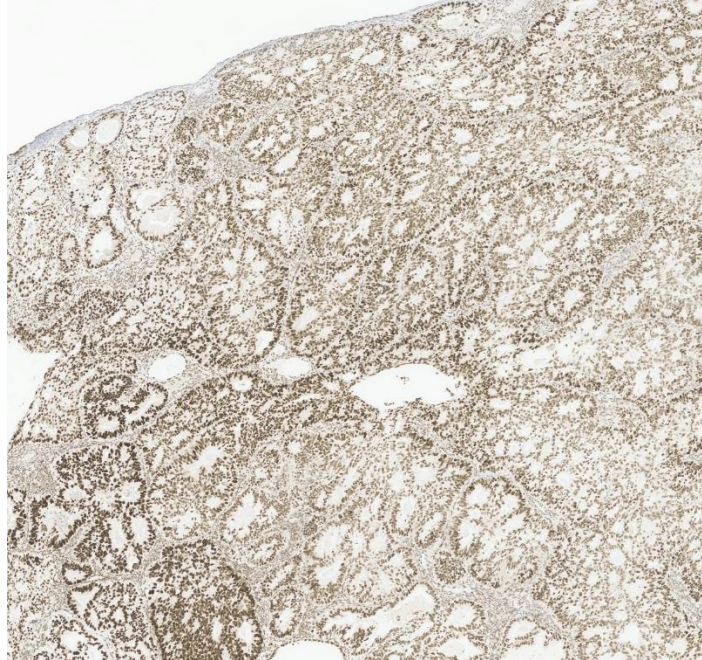
MLH1



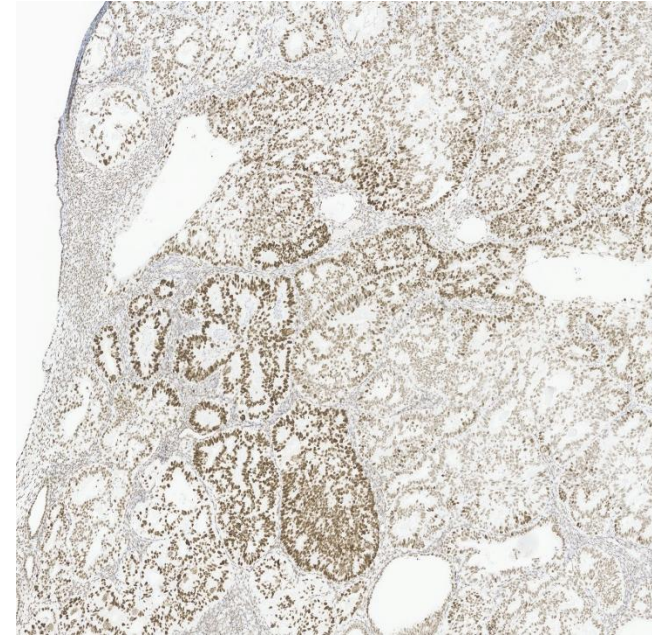
PMS2



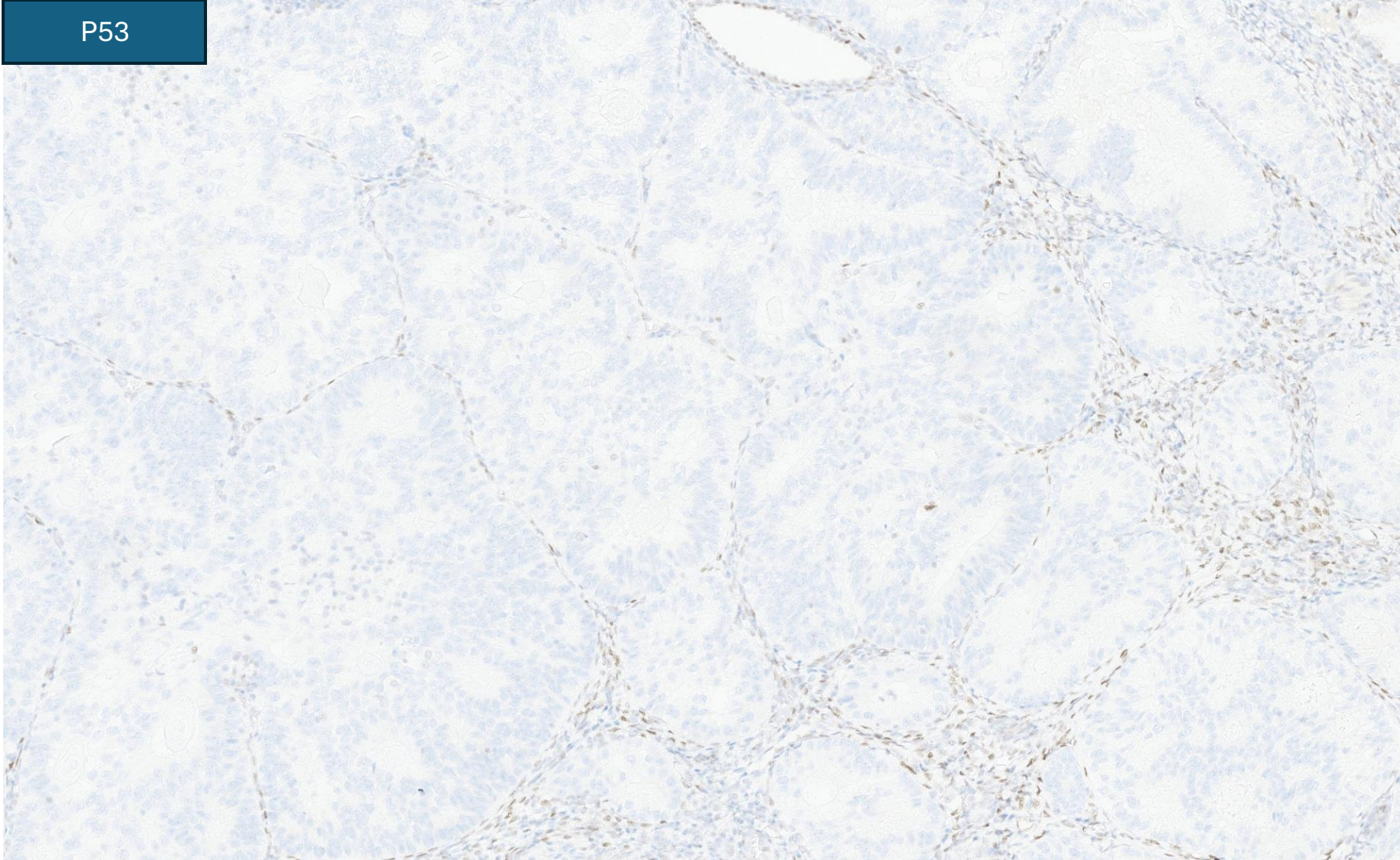
MSH2



MSH6



P53



Surgical pathology diagnosis without MC

- Endometrial carcinoma, consistent with endometrioid carcinoma, FIGO grade 2 with p53 IHC abnormality
- Carcinoma shows superficial myometrial invasion (<10%) with no LVSI; other parts are negative
- The preliminary 2023 FIGO stage is IA2.

RESULT

The results provided within this report represent molecular testing results only. Please refer to the Surgical Pathology report for the integrated molecular and pathology diagnosis (if applicable).

Provided diagnosis: endometrial carcinoma

Microsatellite Instability (MSI) status: Stable (MSS)

The following CLINICALLY RELEVANT VARIANT was detected:
Gene: TP53
DNA Change: c.595G>T (Exon 6)
Amino Acid Change: p.G199* (Gly199*)
Variant Allele Frequency: 20%

The following VARIANT OF UNCERTAIN SIGNIFICANCE was detected:
Gene: L1CAM
DNA Change: c.2039C>T (Exon 17)
Amino Acid Change: p.S680L (Ser680Leu)
Variant Allele Frequency: 4.7%

No other reportable sequence variants were detected within the analyzed regions of the tested gene(s) listed in the method description.

This test does not include NTRK fusion testing. Clinically approved therapy is available for patients with metastatic or unresectable solid tumors with an NTRK fusion [fda.gov/drugs]. If clinically indicated, consider NTRK Gene Fusion Panel (NTRK) for evaluation of NTRK fusions. Please refer to mayocliniclabs.com or call 1 800-533-1710 for more information.

INTERPRETATION

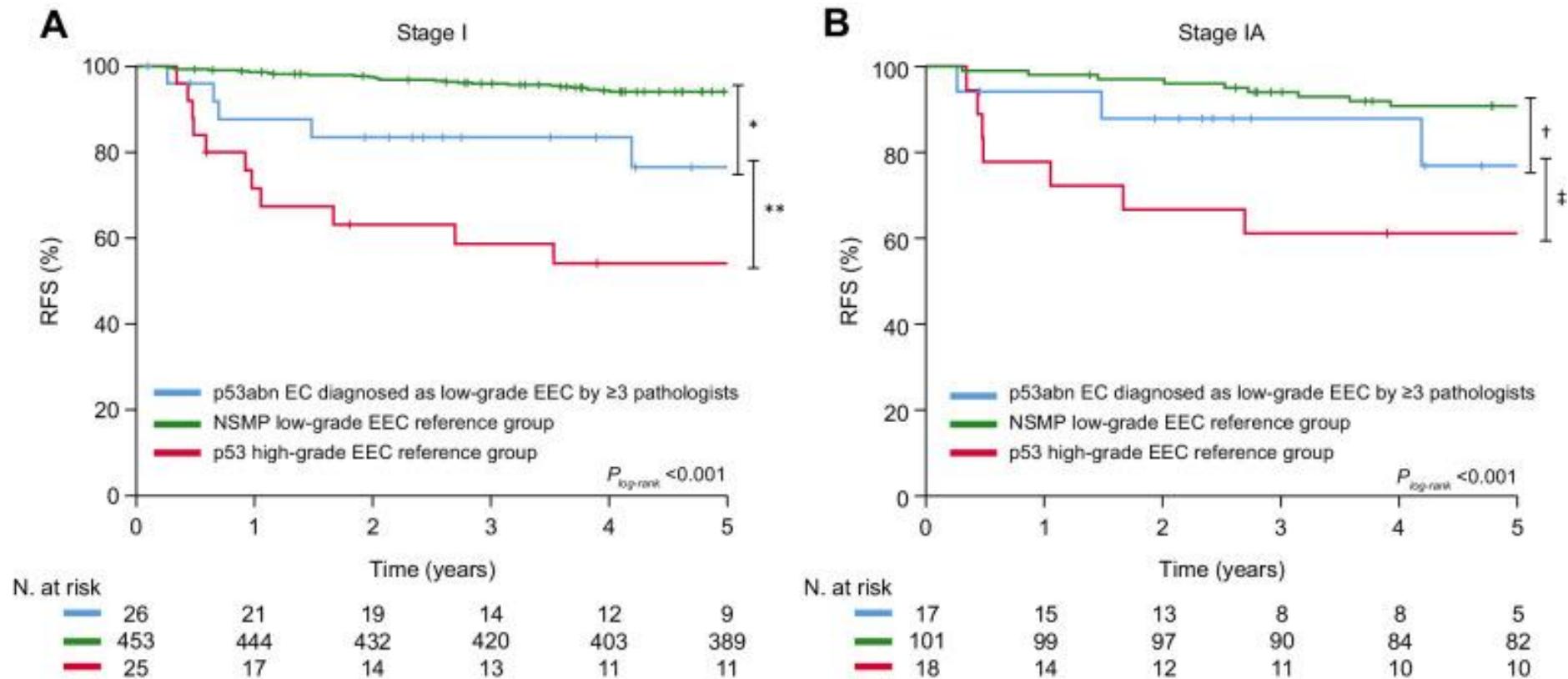
MSI: Stable (MSS)

NO evidence of microsatellite instability was detected suggesting the presence of normal DNA mismatch repair function within the tumor. Current data suggest that advanced stage solid tumors with intact mismatch repair (MSS) are less likely to be responsive to treatment with immunotherapies such as anti-PD-1 therapies [PMID 28596308, PMID 29355075].

However, lenvatinib in combination with pembrolizumab has been FDA-approved for patients with advanced endometrial carcinoma with intact mismatch repair (MSS) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation [PMID: 32167863, PMID: 32295834].

The final FIGO stage with MC is Stage IICmp53abn

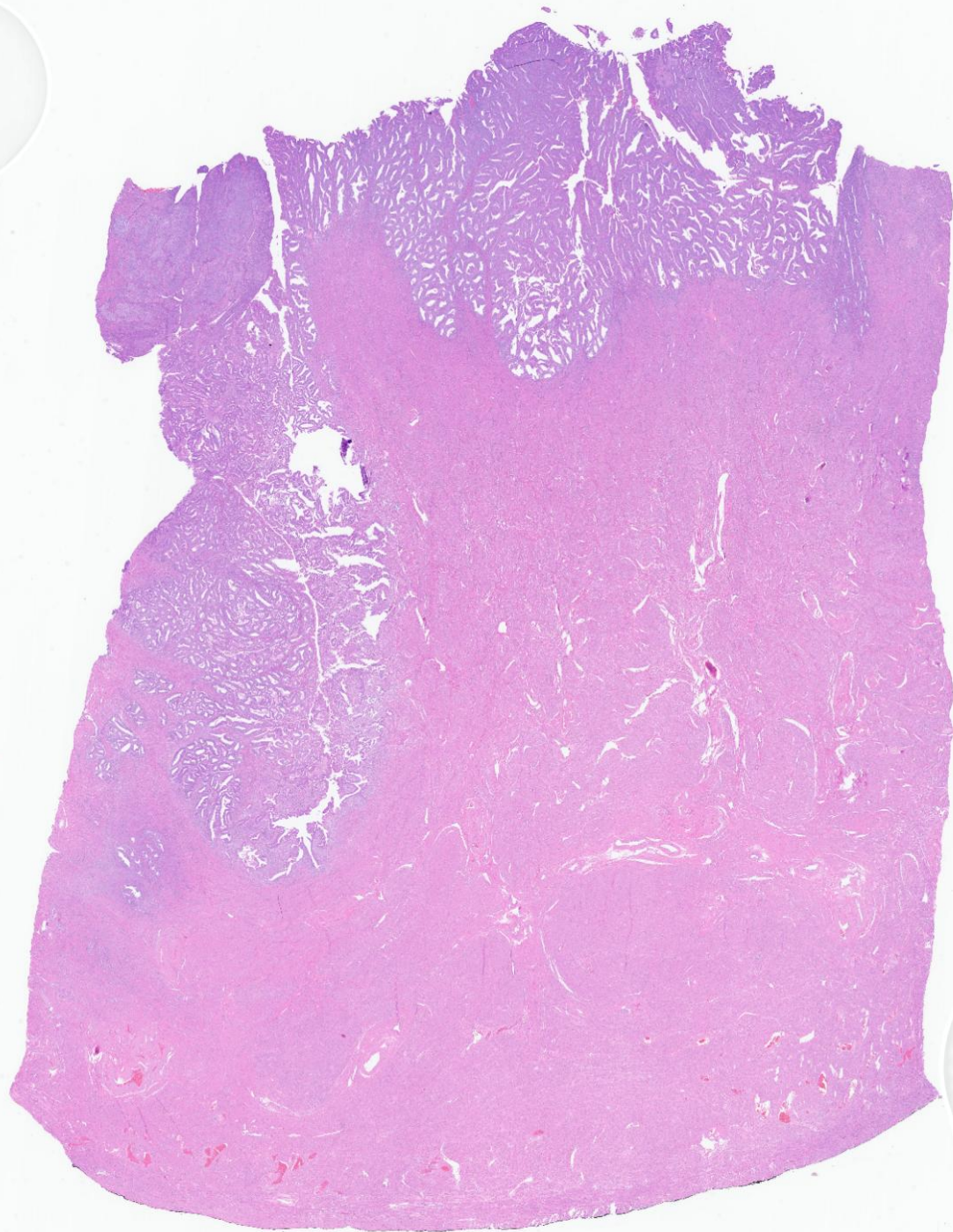
Prognosis of FIGO stage 1 p53 abnormal low grade endometrioid endometrial carcinomas



Jamieson et al. Clinical Cancer Res. 2023

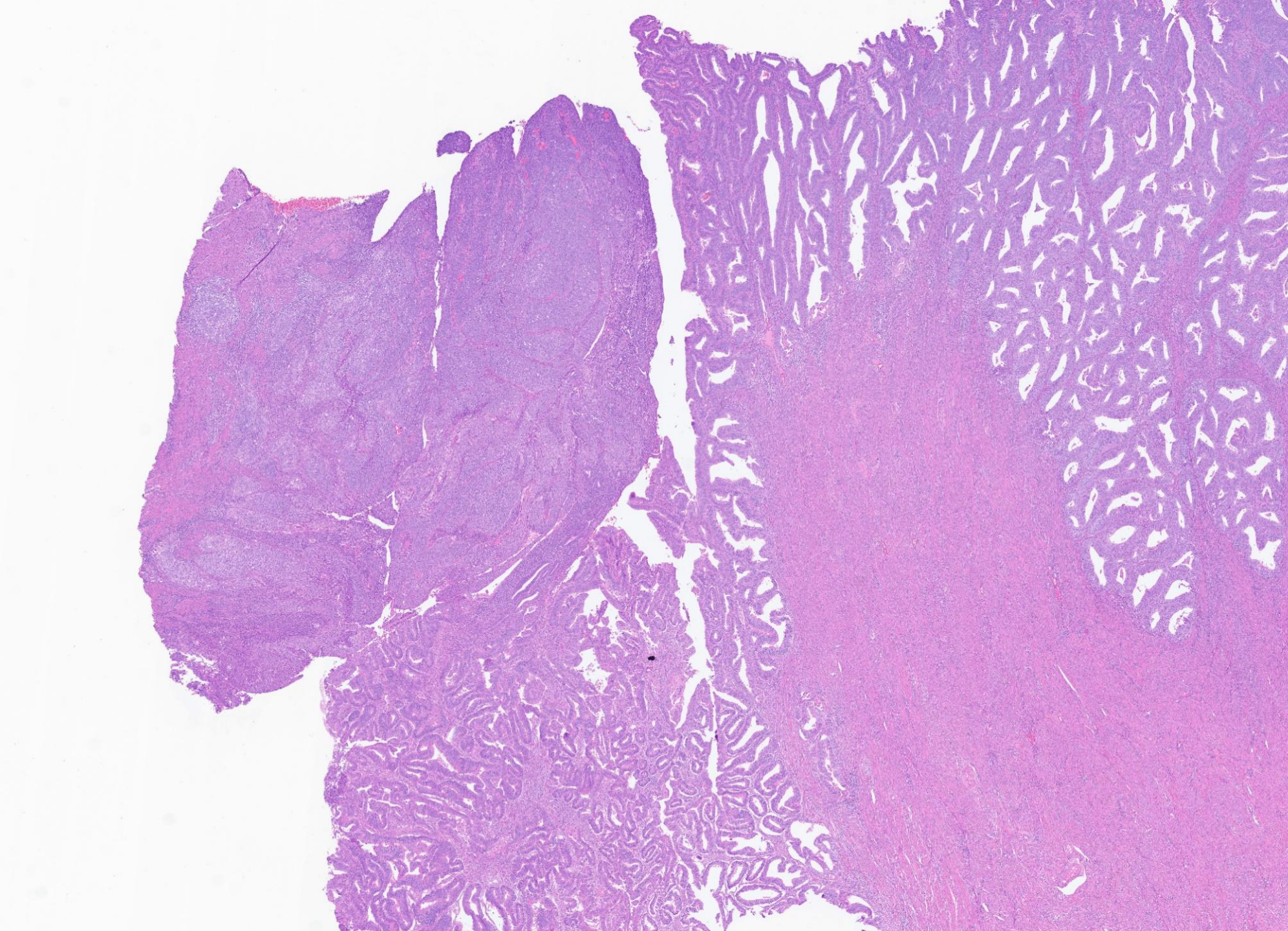
Case 2

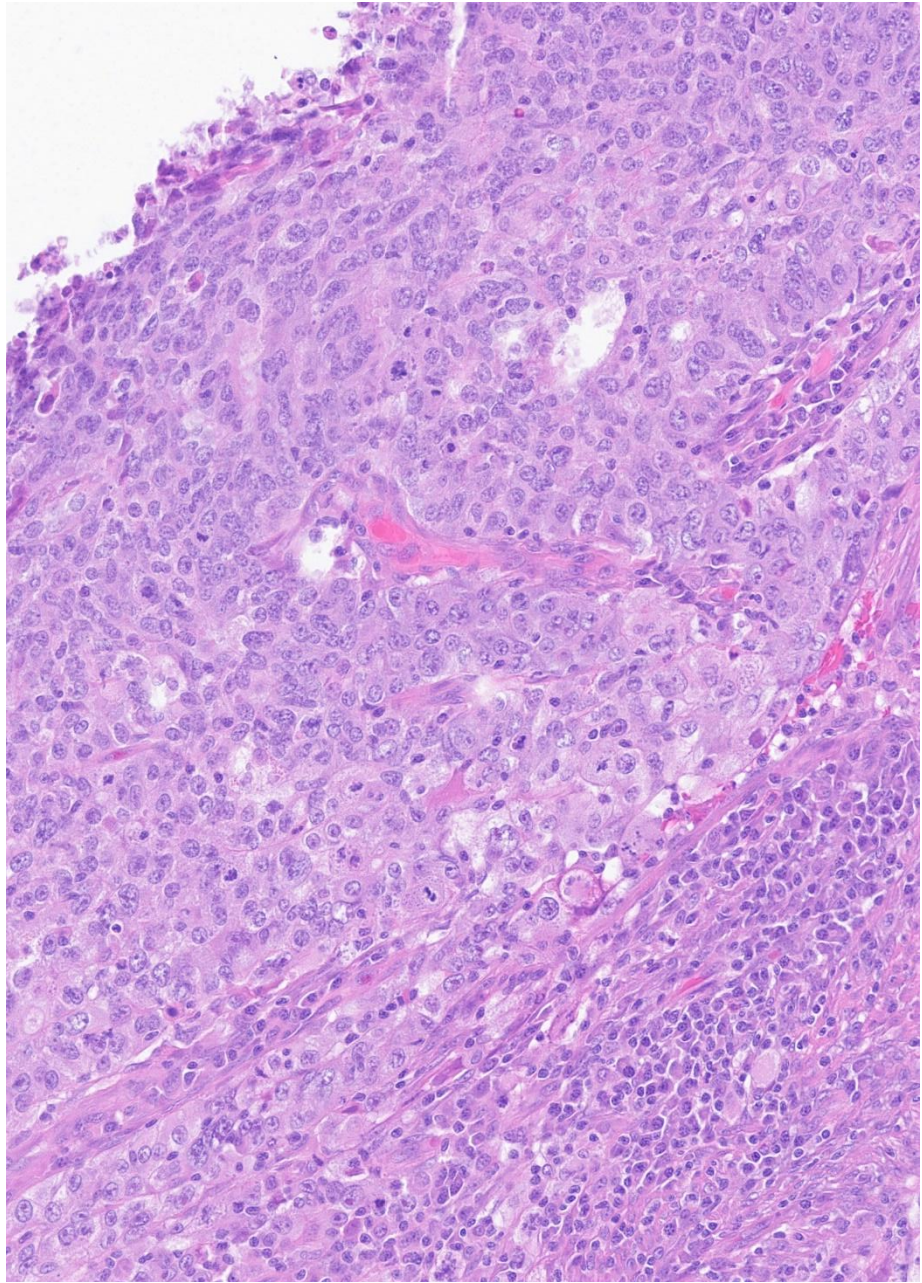
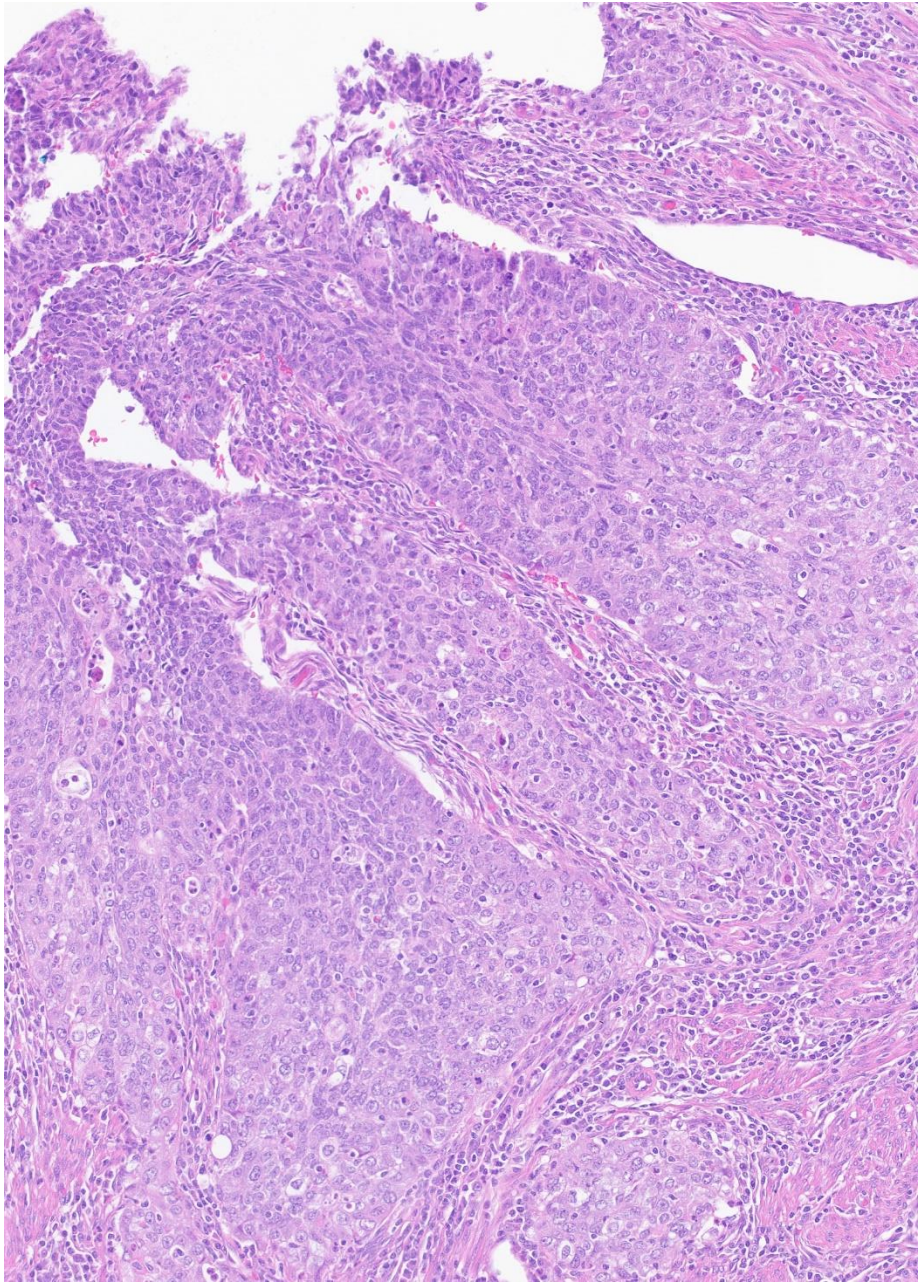
- A 58-year-old patient with post-menopausal bleeding
- Endometrial biopsy showed FIGO grade 1 endometrioid adenocarcinoma
- A hysterectomy along with SLN were performed

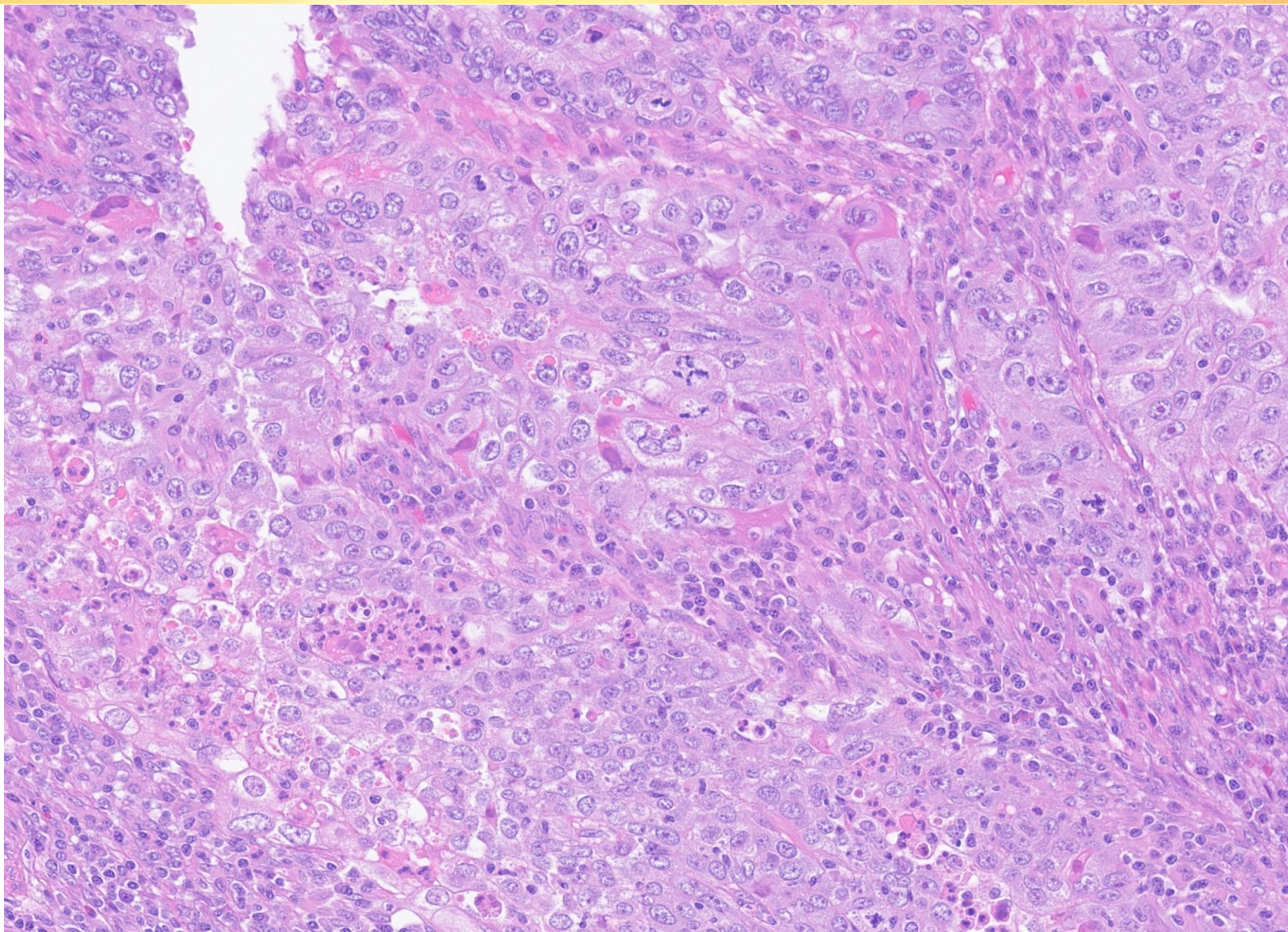




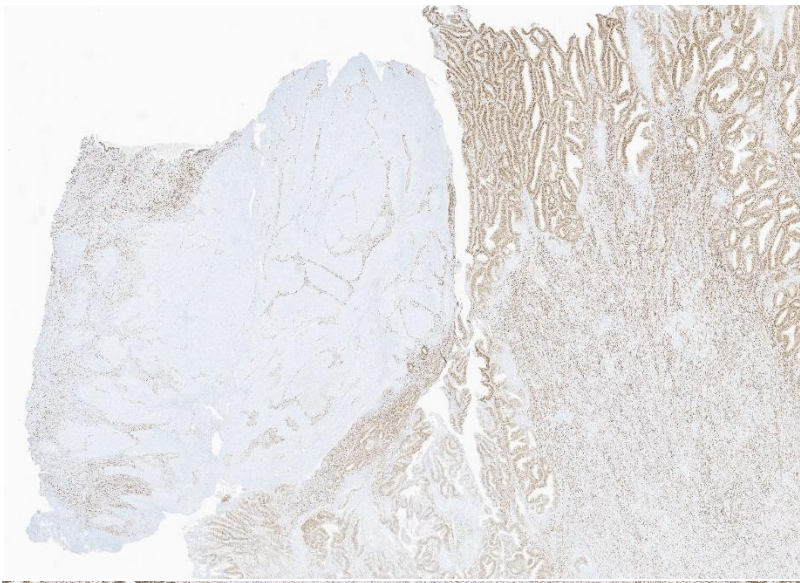
#AAPAfall26



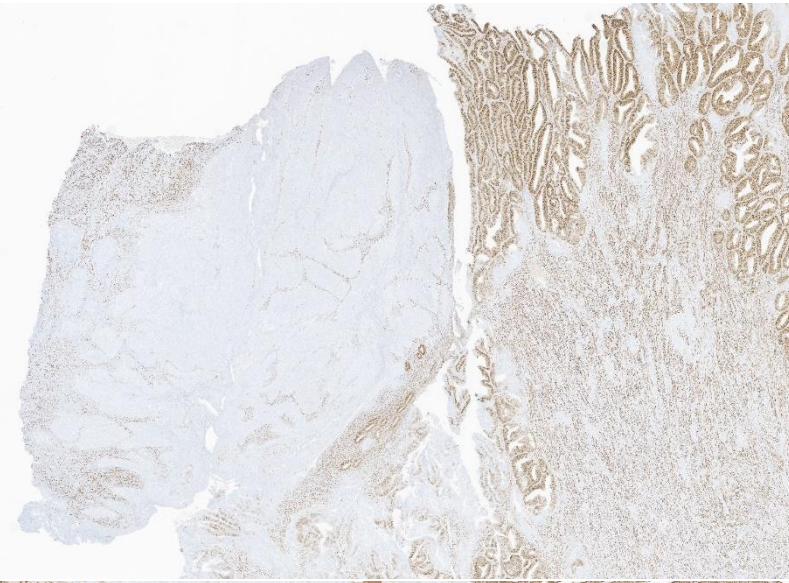




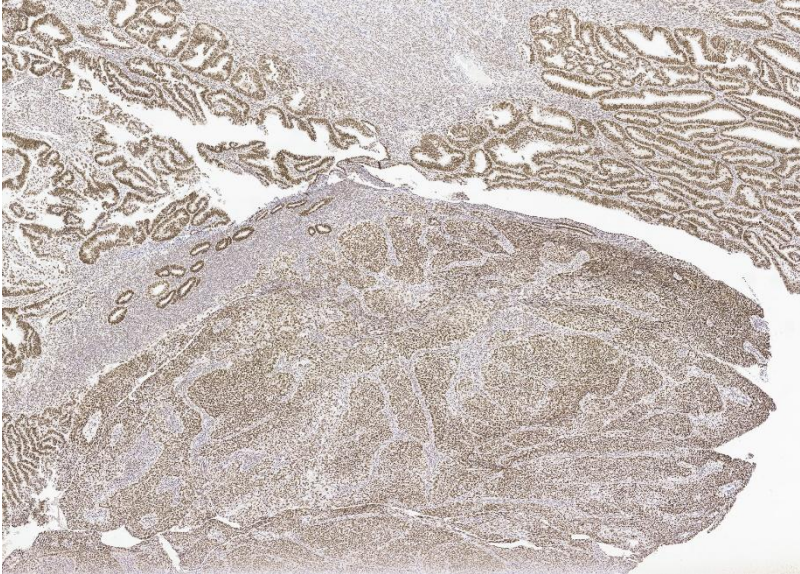
ER



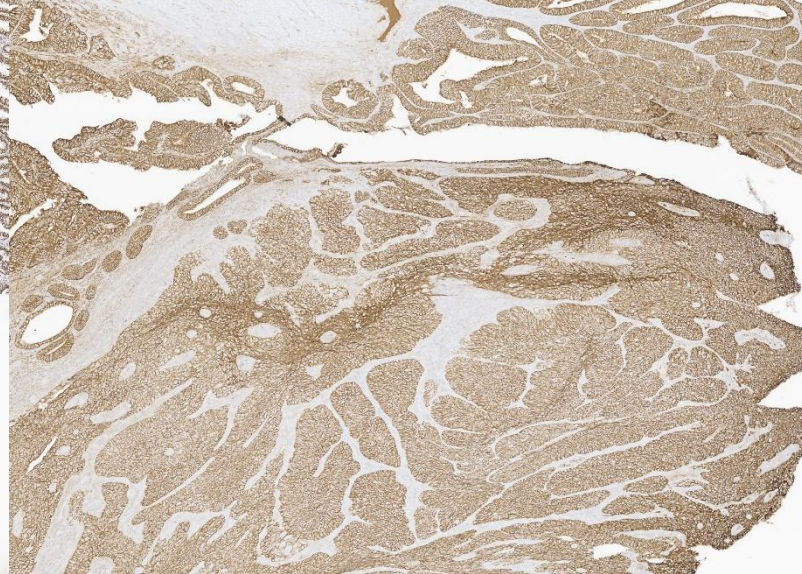
PR



BRG1

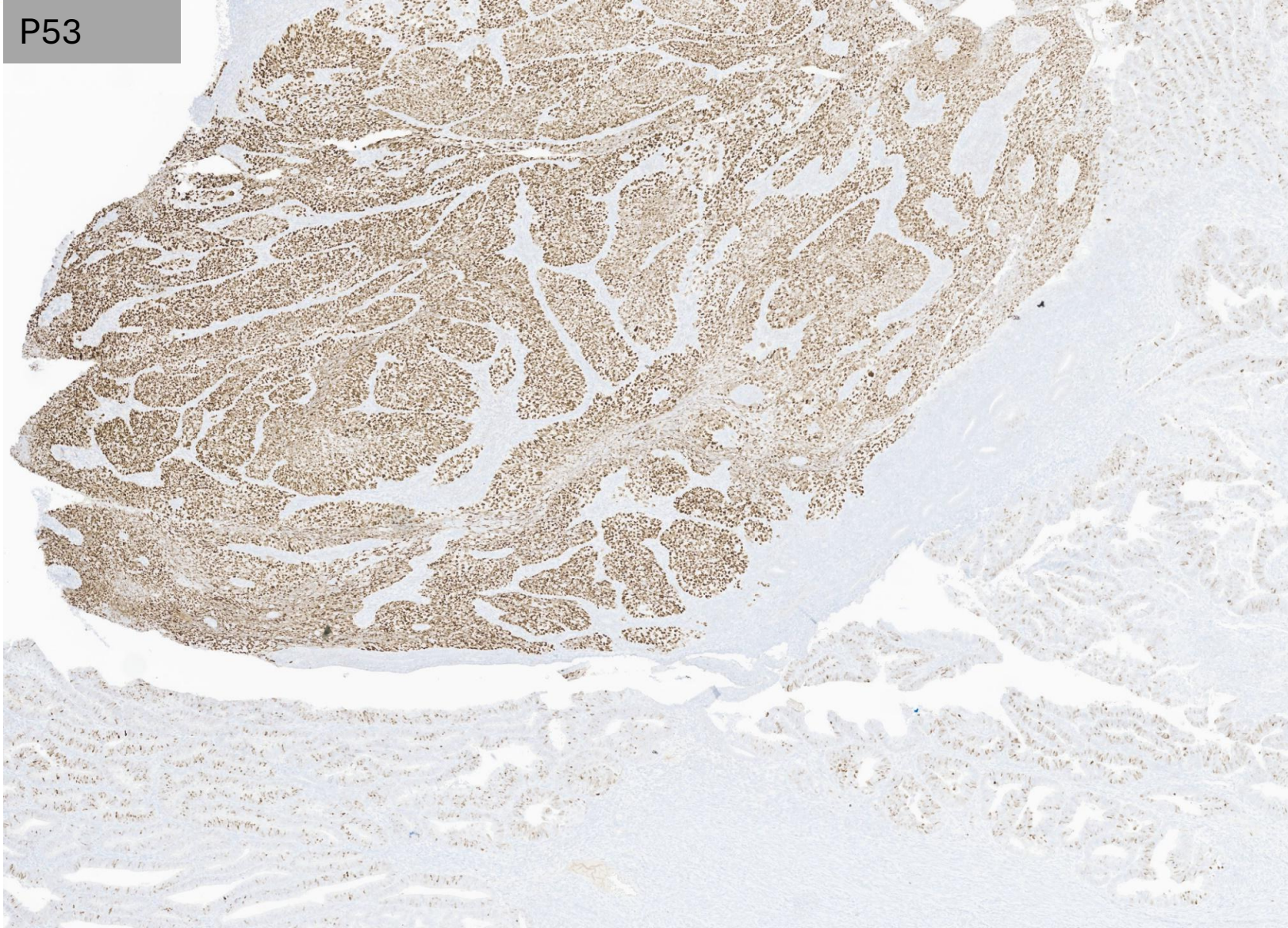


ECad



MMR proteins retained

P53



Surgical pathology diagnosis without MC

- Endometrial carcinoma, favor high grade endometrial carcinoma with p53 mutation (MMR proteins retained)
- Carcinoma shows myometrial invasion ($>1/2$) without LVSI; other parts are negative
- The preliminary 2023 FIGO stage is IIC.

RESULT

Provided diagnosis: Endometrial carcinoma

The following CLINICALLY RELEVANT VARIANTS were detected:

Gene: **POLE**

DNA Change: c.890C>T (Exon 9)

Amino Acid Change: p.S297F (Ser297Phe)

Variant Allele Frequency: 23.8%

Gene: MSH6

DNA Change: c.3964G>T (Exon 9)

Amino Acid Change: p.E1322* (Glu1322*)

Variant Allele Frequency: 17.3%

Gene: **TP53**

DNA Change: c.581T>G (Exon 6)

Amino Acid Change: p.L194R (Leu194Arg)

Variant Allele Frequency: 3.9%

Gene: TP53

DNA Change: c.637C>T (Exon 6)

Amino Acid Change: p.R213* (Arg213*)

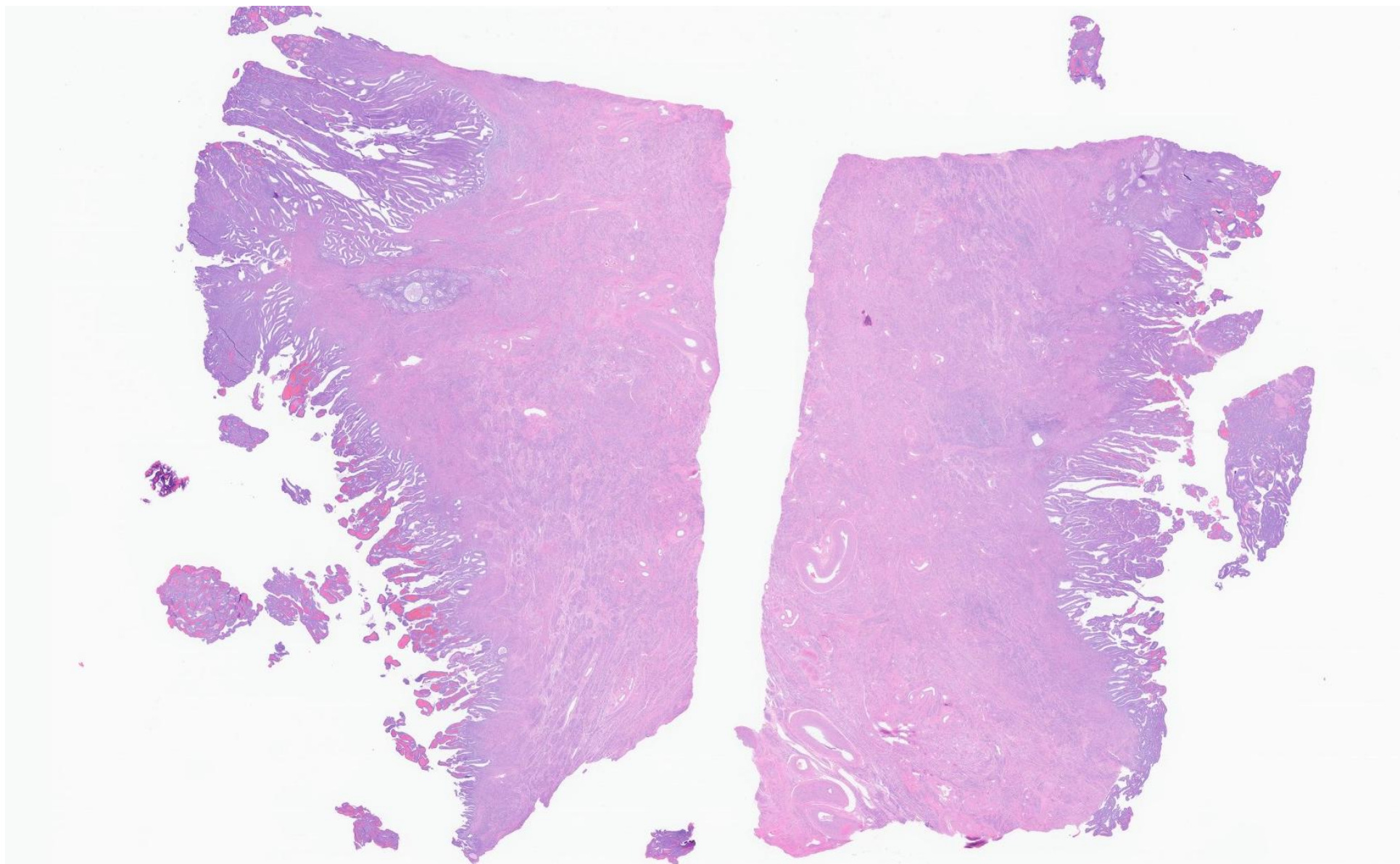
Variant Allele Frequency: 5.7%

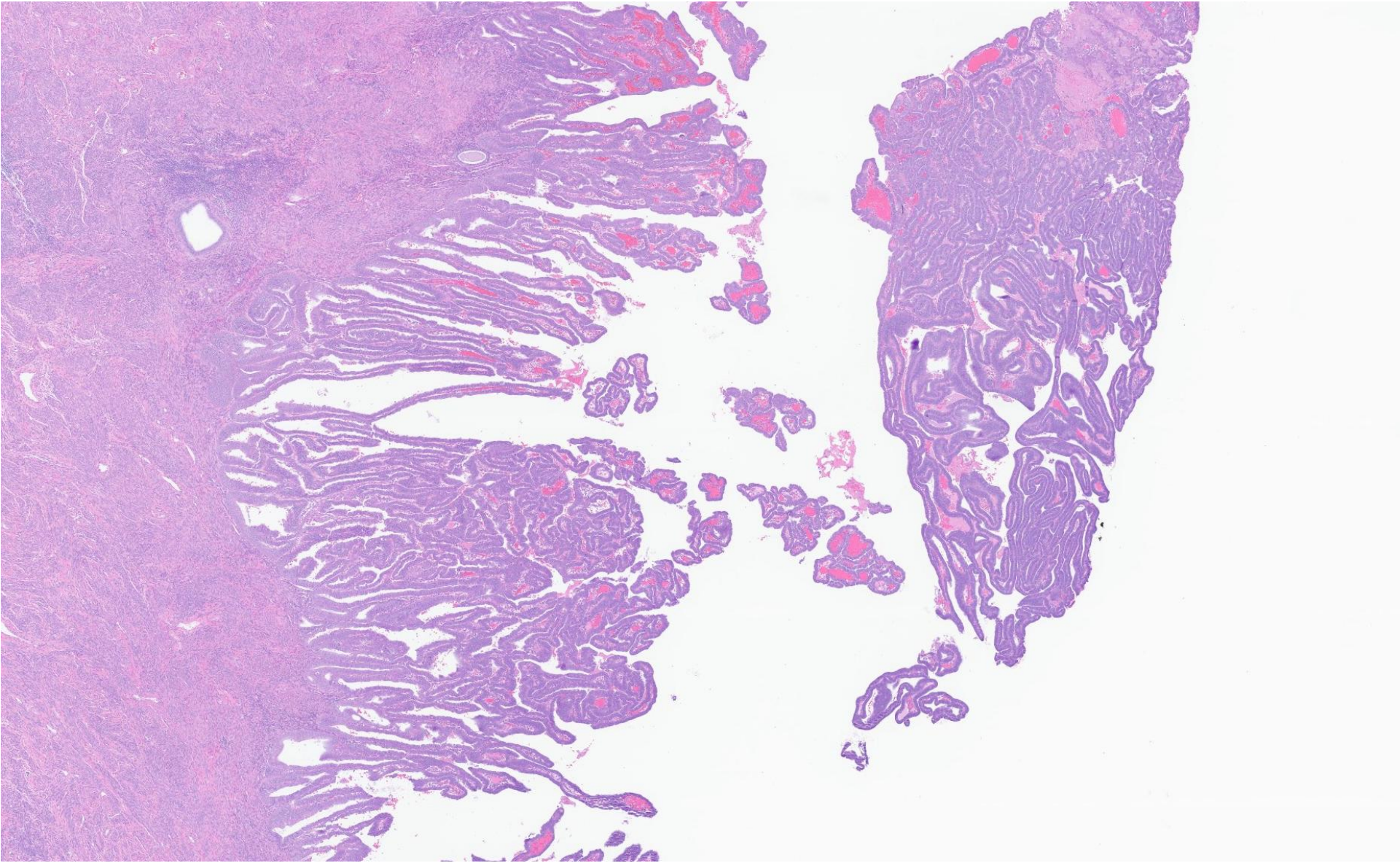
Microsatellite Instability (MSI) status: Stable (MSS)

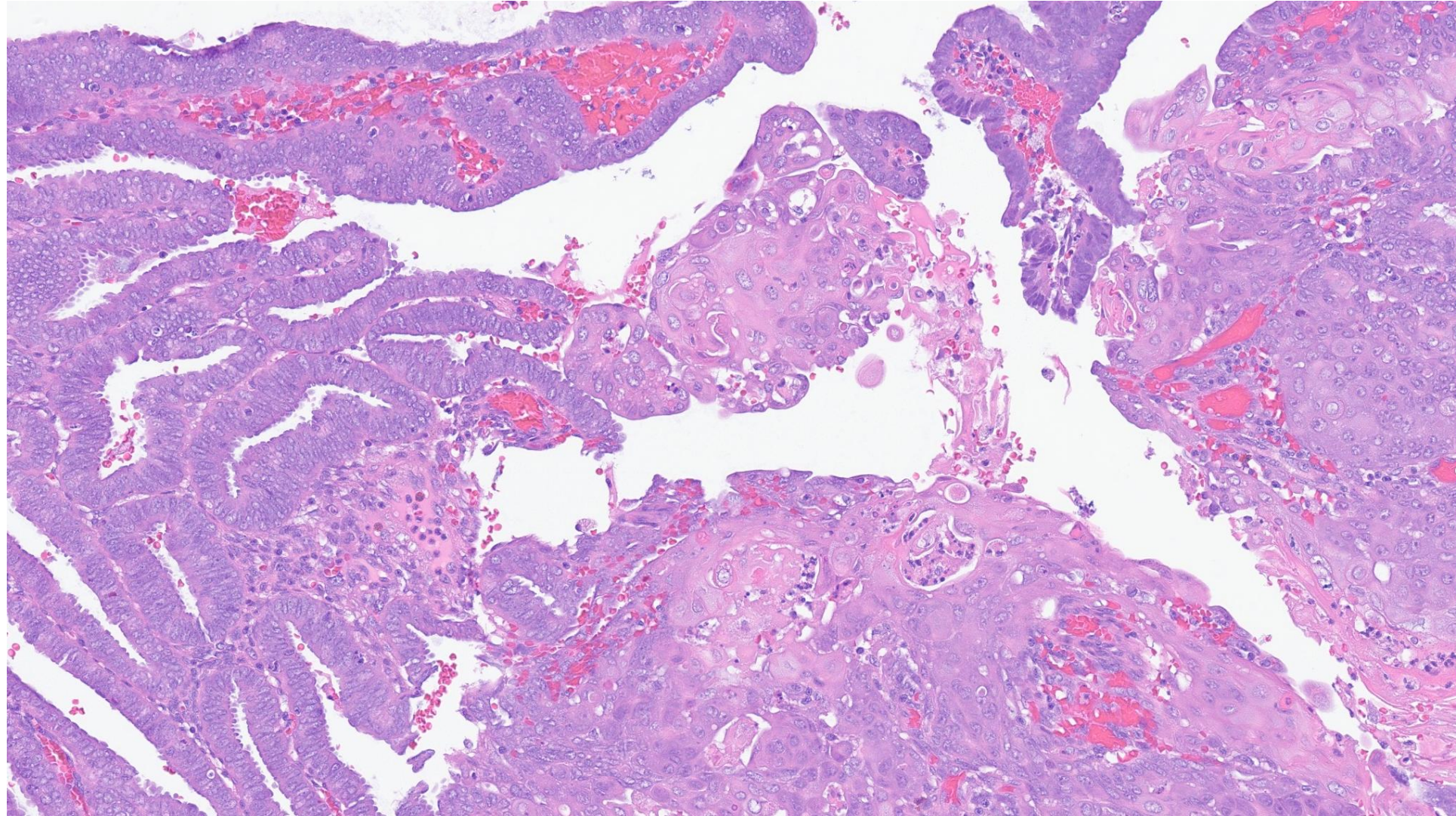
The final FIGO stage with MC is Stage IAmPOLEmut

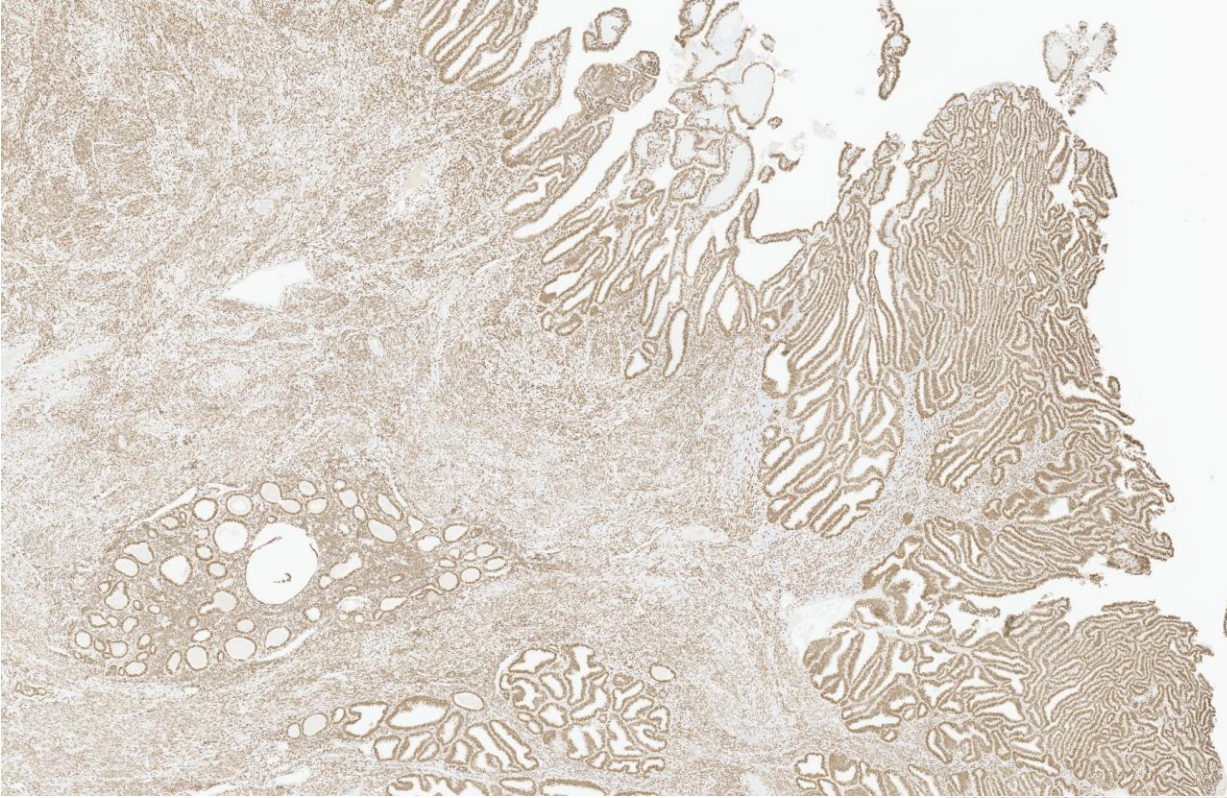
Case 3

- A 73-year-old patient with post-menopausal bleeding
- Endometrial biopsy showed FIGO grade 1 endometrioid carcinoma
- A hysterectomy with SLN was performed

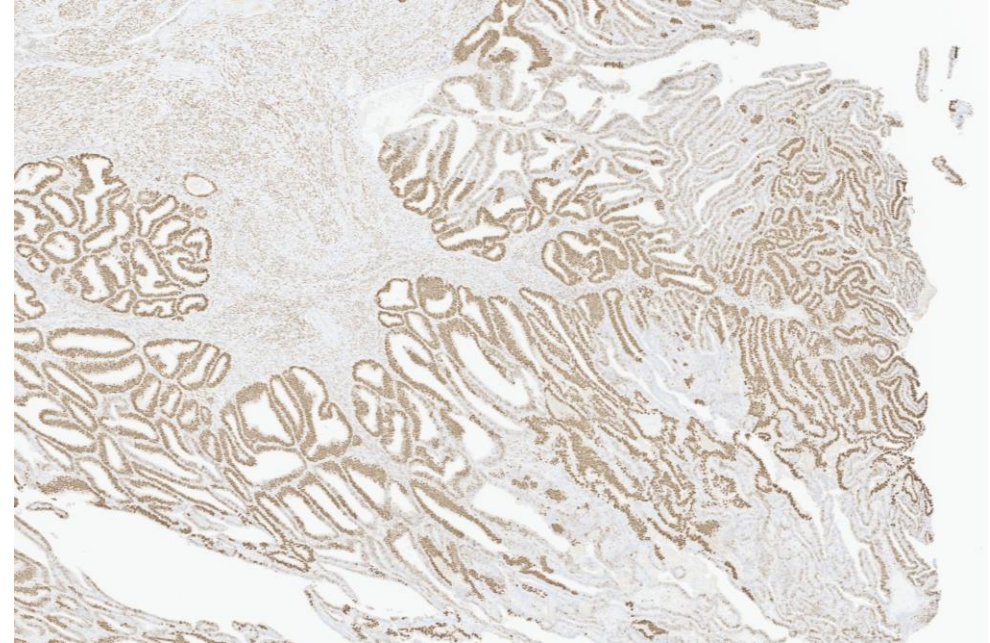






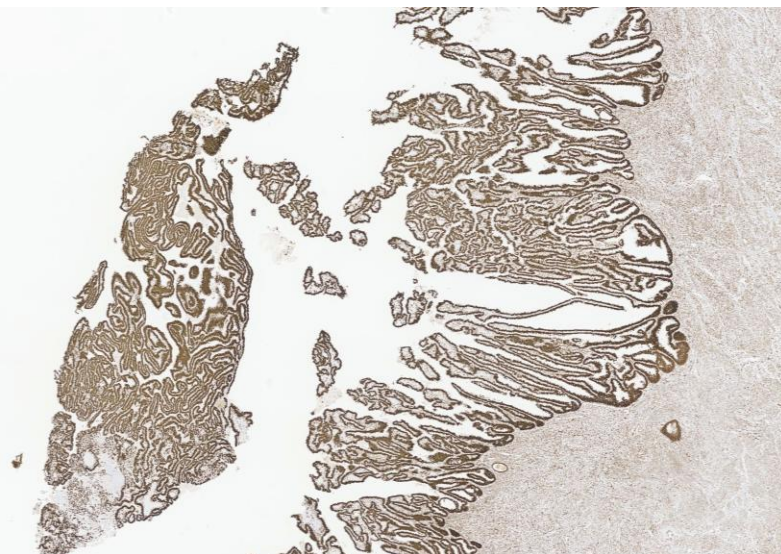


ER

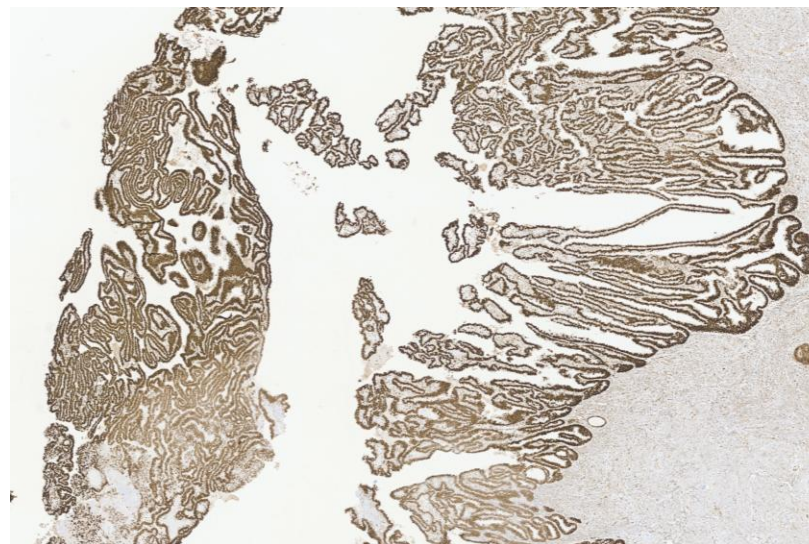


PR

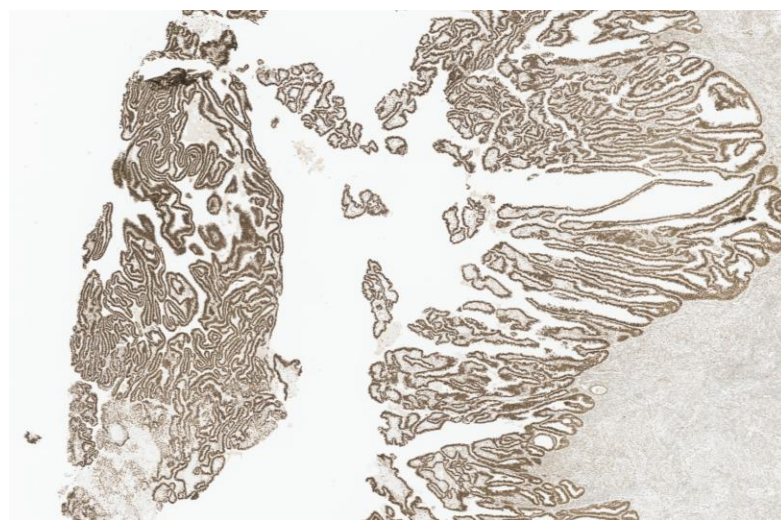
MLH1



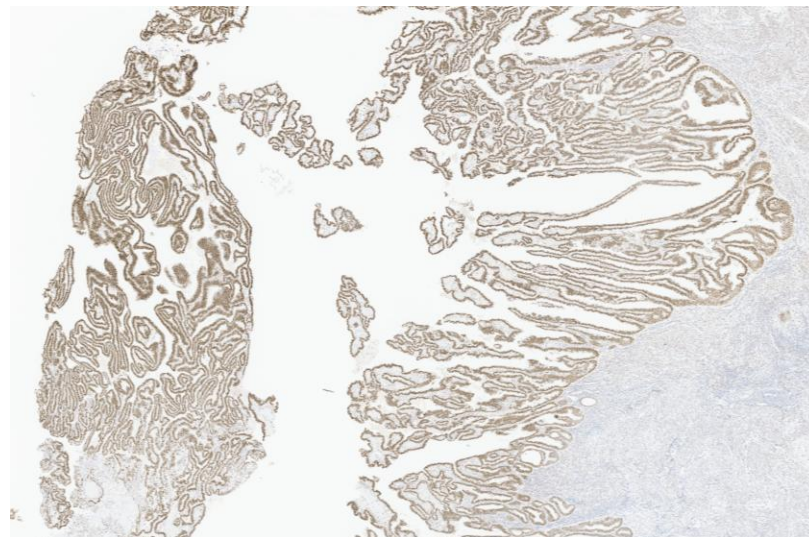
PMS2



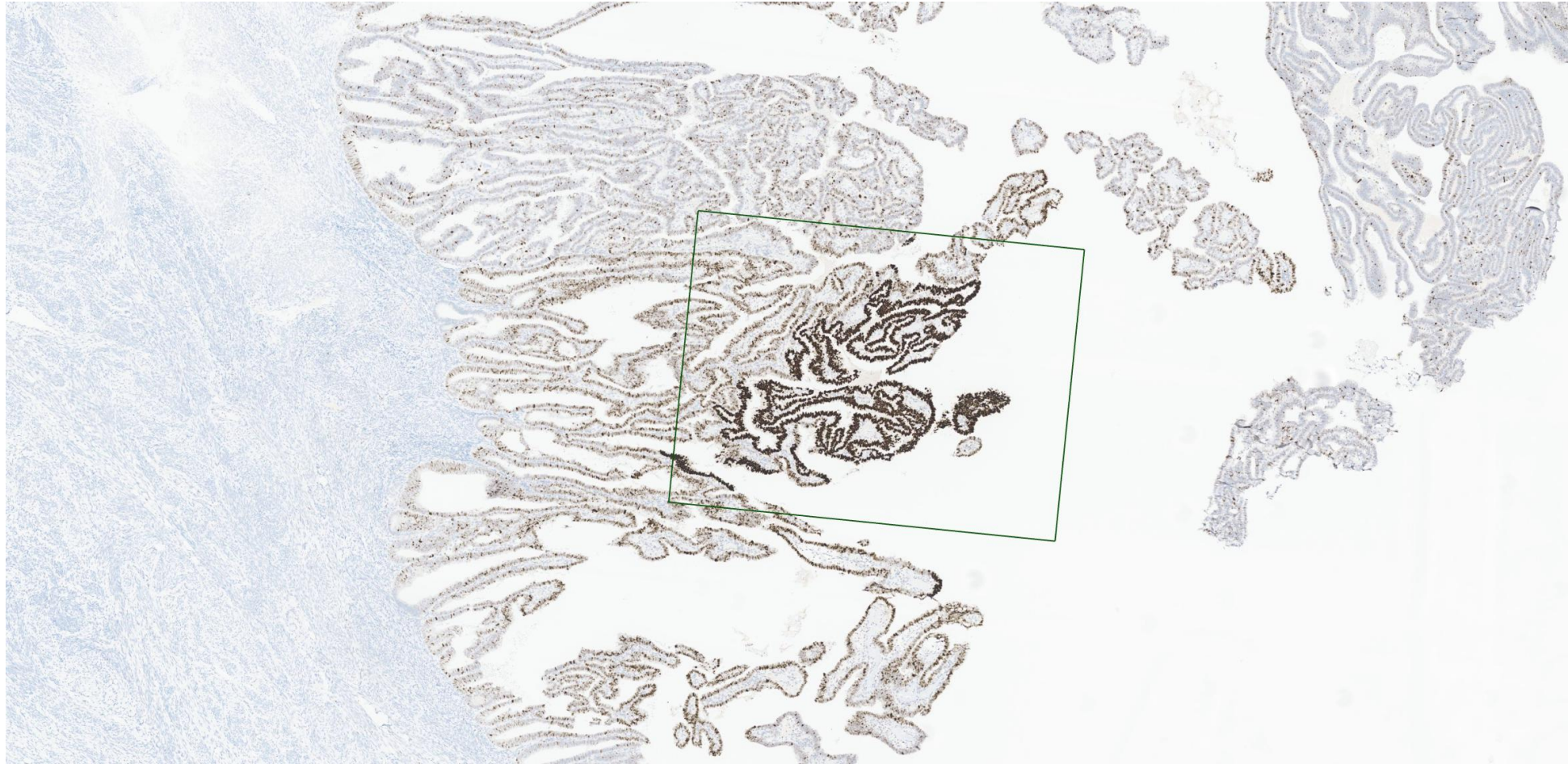
MSH2



MSH6

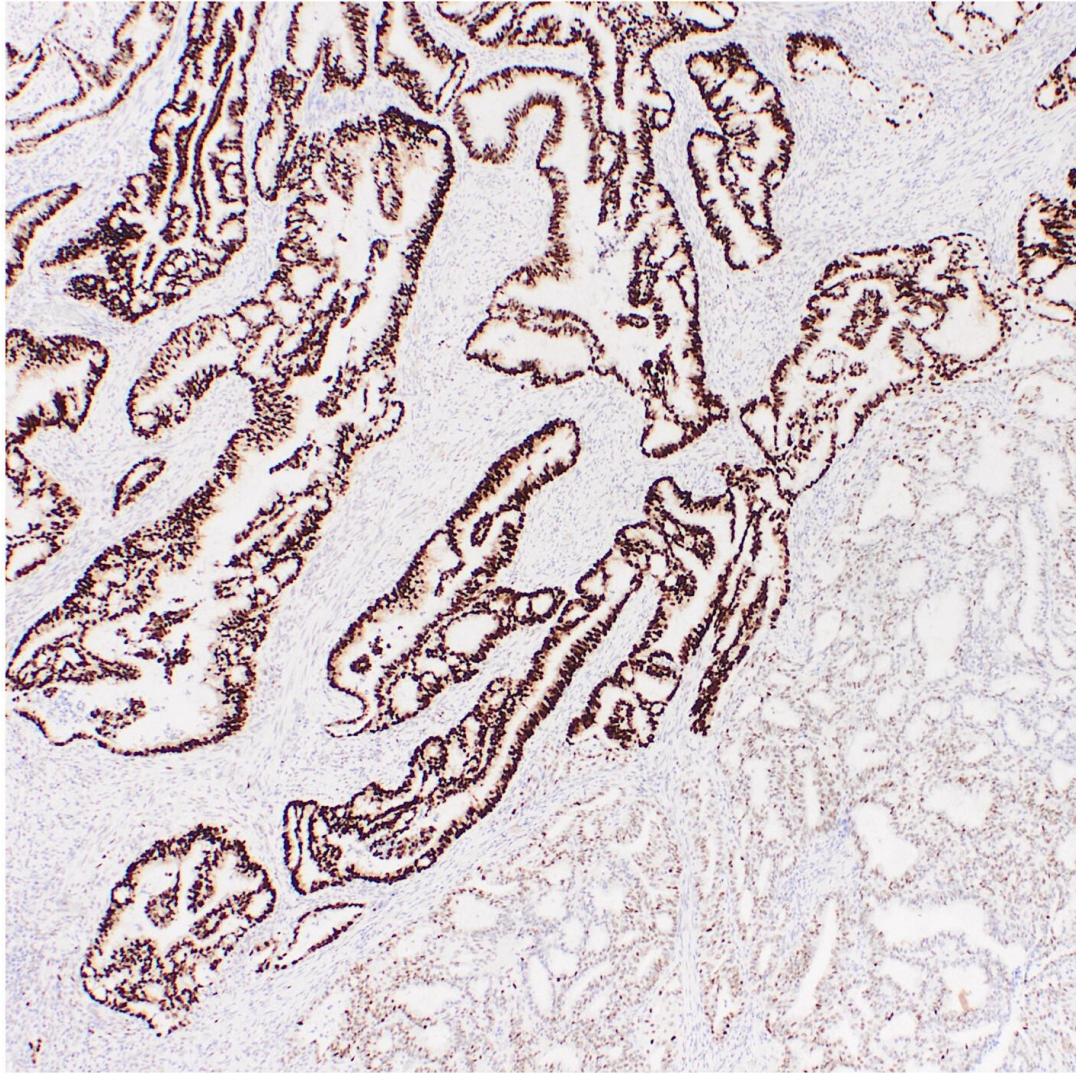


p53



Surgical pathology diagnosis

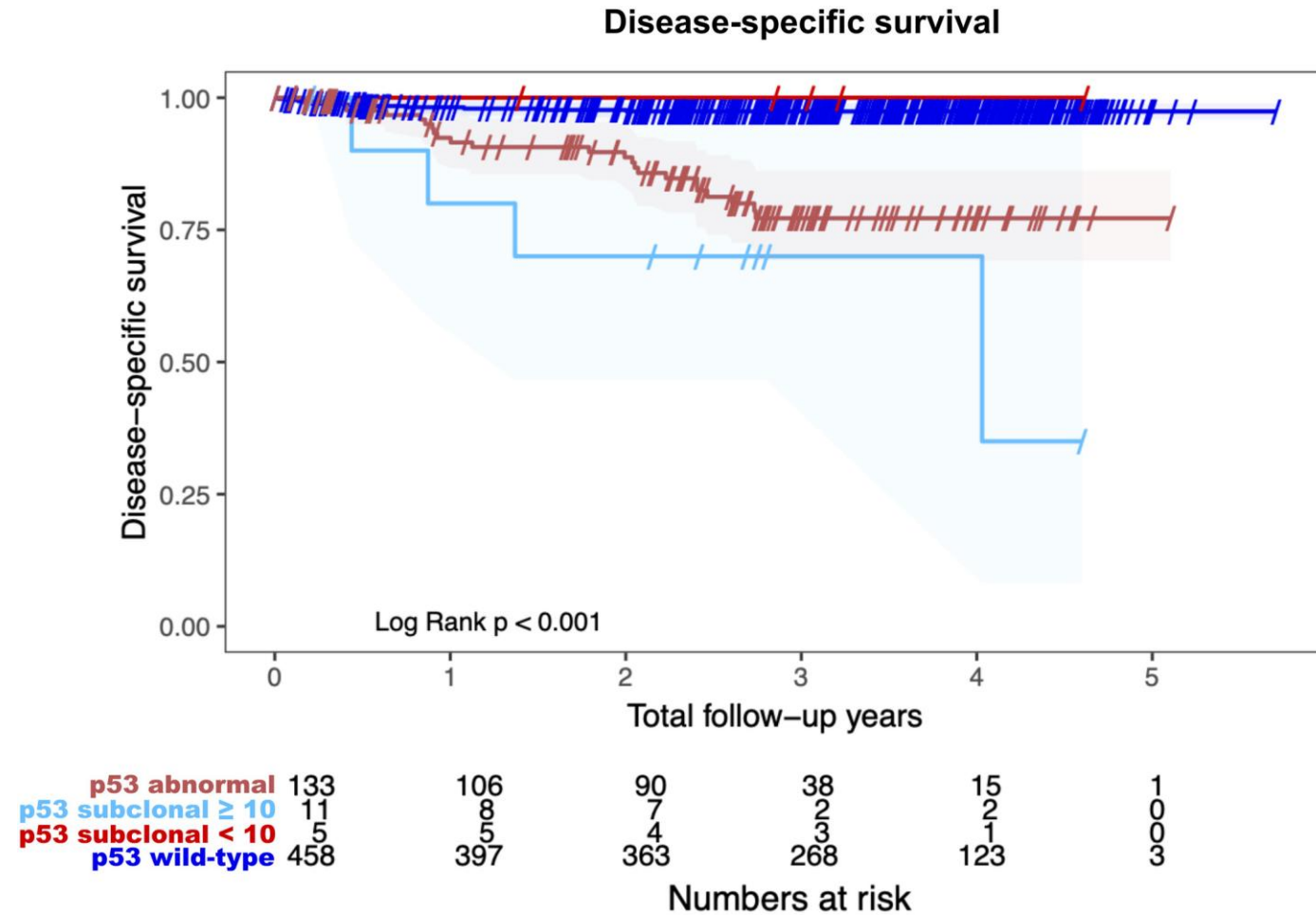
- Endometrial carcinoma, consistent with FIGO grade 1 endometrioid carcinoma with p53 sub-clonal mutation (<10%)
- Carcinoma shows superficial myometrial invasion (<20%), no LVSI; other parts are negative
- The preliminary 2023 FIGO stage is IA2, pending molecular classification.



WHAT IS P53 SUB-CLONAL MUTATION ENDOMETRIAL CARCINOMA?

- Huvila et al. Histopathology 2023; 83:880-890
- 38 of 957 EC showed sub-clonal mutation on IHC
- 23 >10%; 15 <10%
- 22 of 38 cases are multiple classifiers

Prognosis of p53 sub-clonal mutation endometrial cancers



RESULT

The results provided within this report represent molecular testing results only. Please refer to the Surgical Pathology report for the integrated molecular and pathology diagnosis (if applicable).

Provided diagnosis: endometrial adenocarcinoma

Microsatellite Instability (MSI) status: Stable (MSS)

The following CLINICALLY RELEVANT VARIANTS were detected:

Gene: CTNNB1

DNA Change: c.110C>T (Exon 3)

Amino Acid Change: p.S37F (Ser37Phe)

Variant Allele Frequency: 3.1%

Gene: FBXW7

DNA Change: c.1495_1504del (Exon 10)

Amino Acid Change: p.G499Qfs*22 (Gly499Glnfs*22)

Variant Allele Frequency: 29.1%

Gene: TP53

DNA Change: c.818G>A (Exon 8)

Amino Acid Change: p.R273H (Arg273His)

Variant Allele Frequency: 31.6%

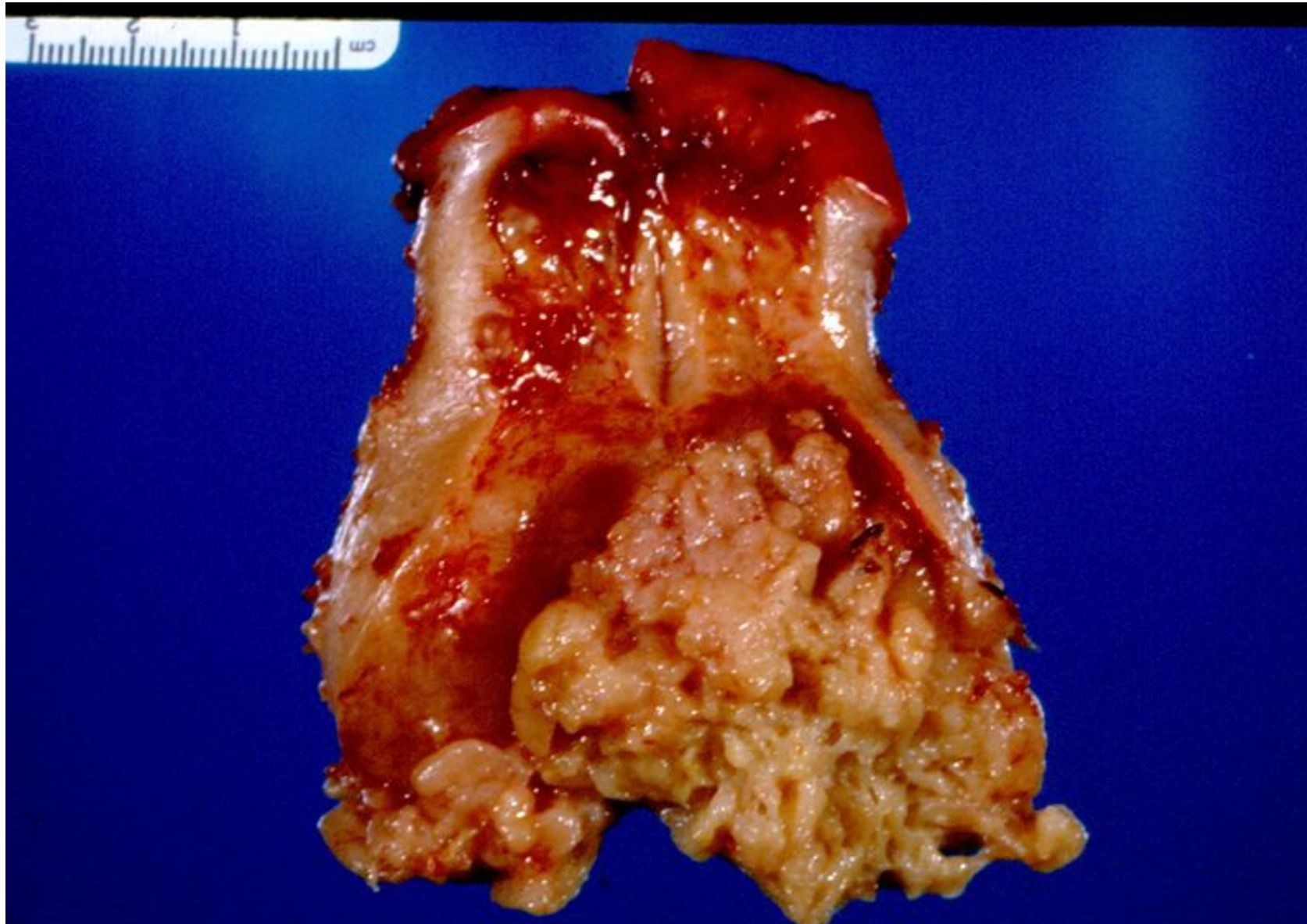
No other reportable sequence variants were detected within the analyzed regions of the tested gene(s) listed in the method description.

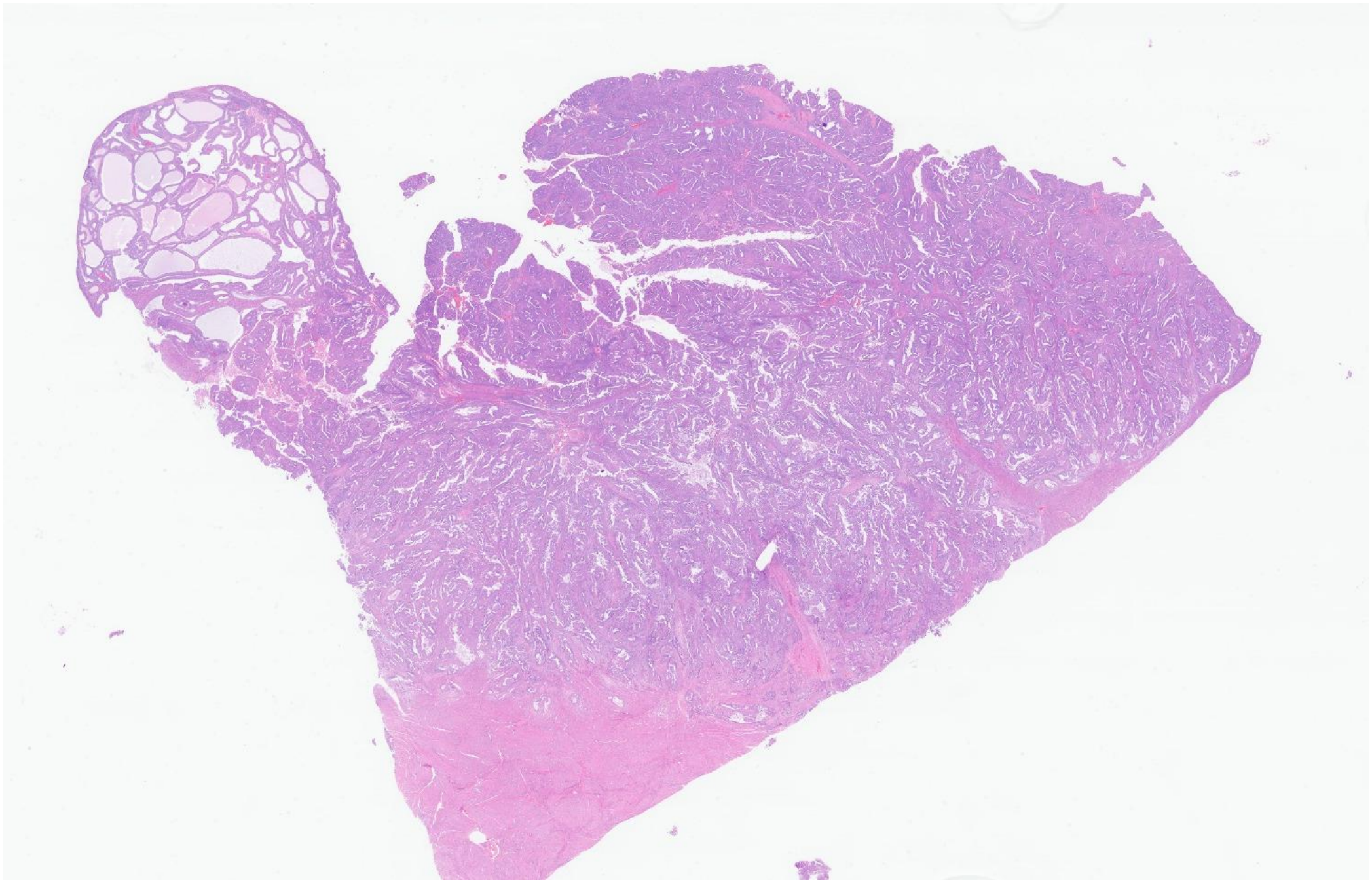
Now what???

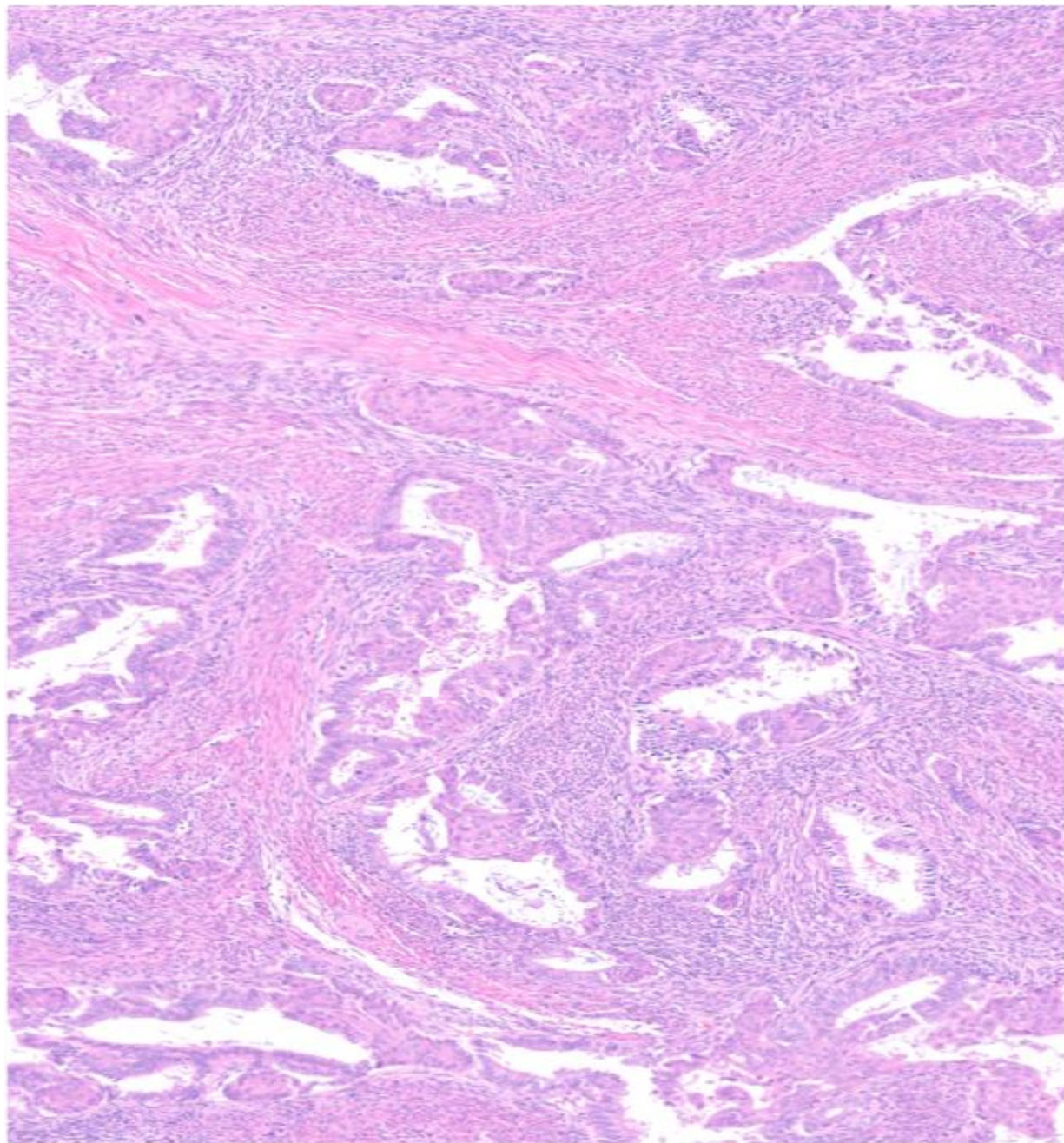
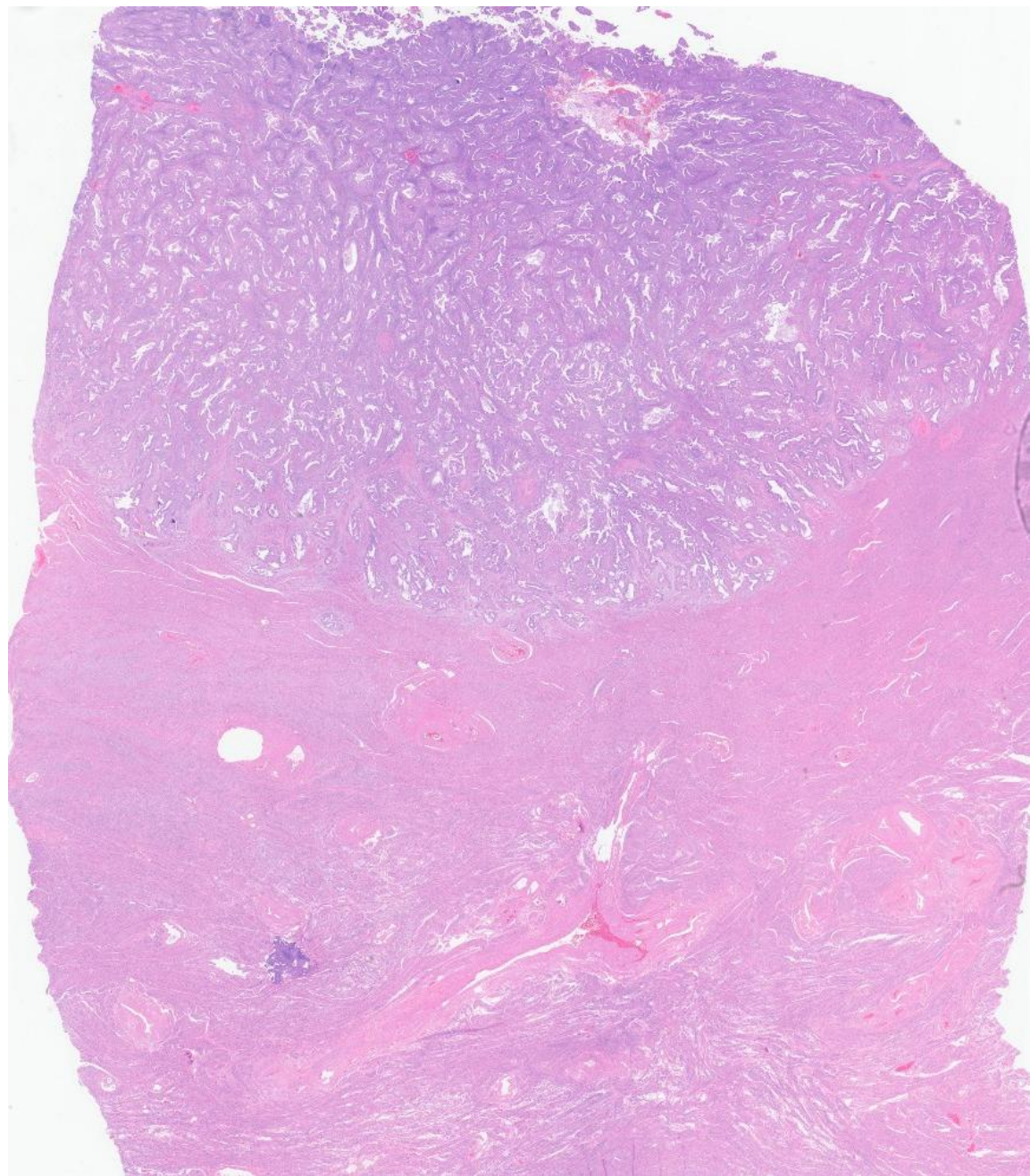
Case 4

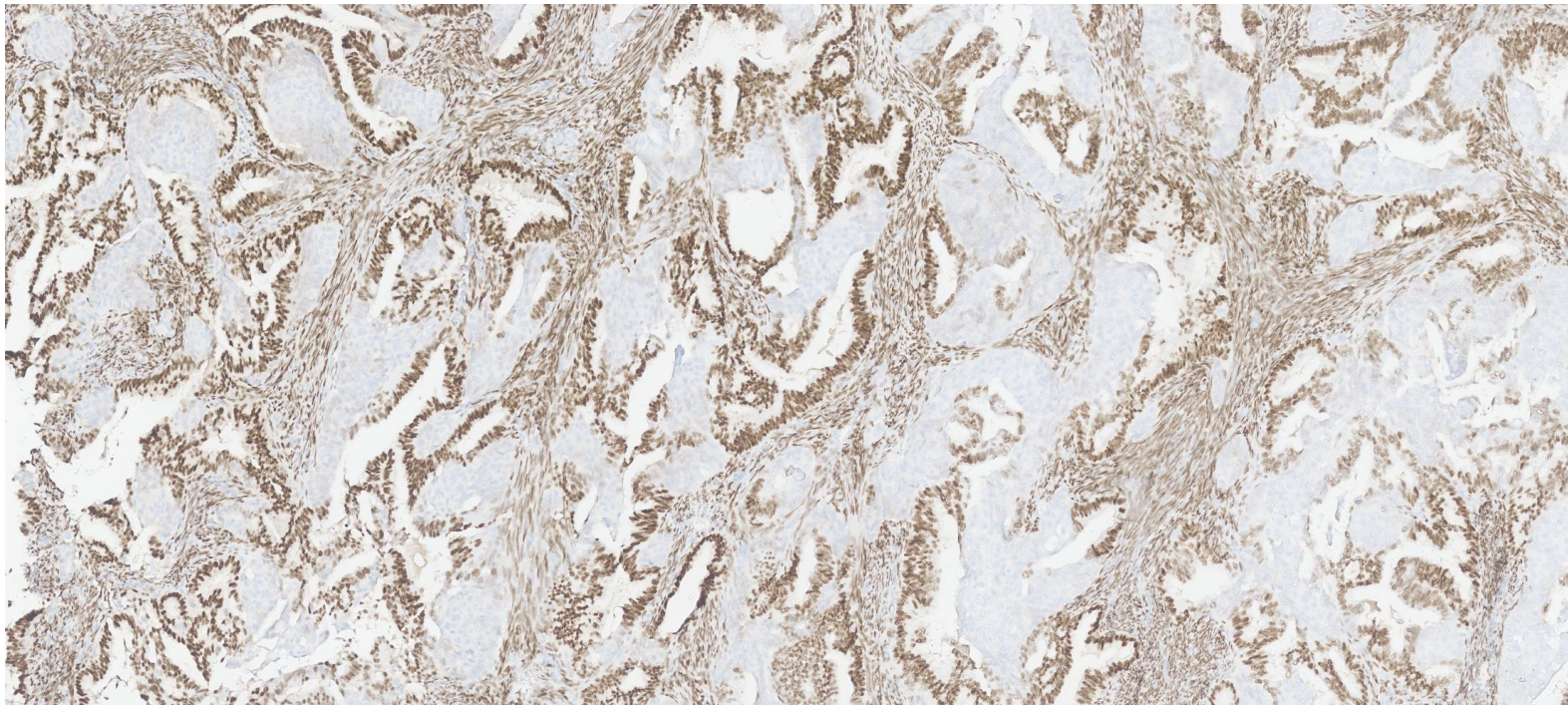
- A 43-year-old patient with abnormal uterine bleeding
- Imaging studies showed an enlarged uterus with cervix and vaginal abnormality
- An endometrial biopsy showed endometrial carcinoma
- A TAH-BSO and sentinel LN excision was performed

Gross Examination

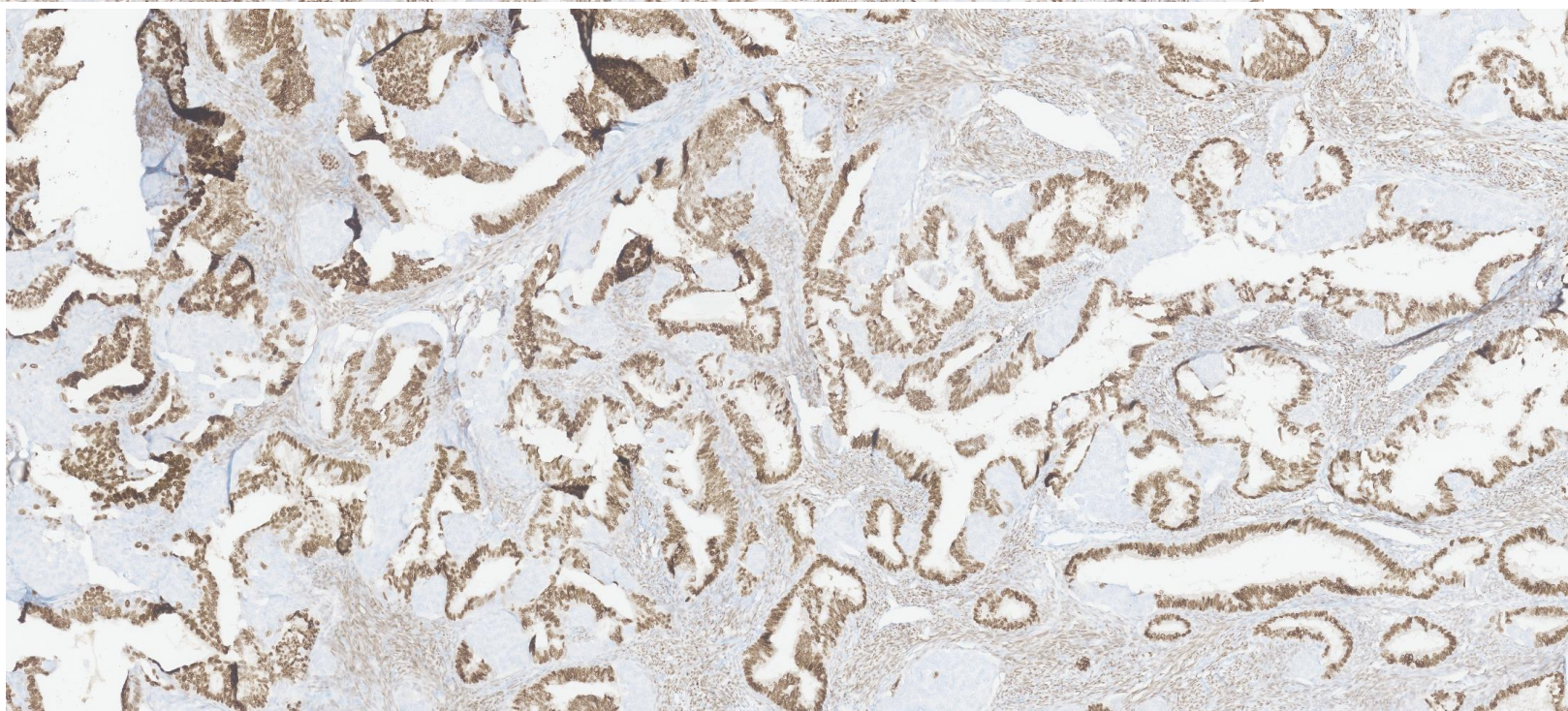






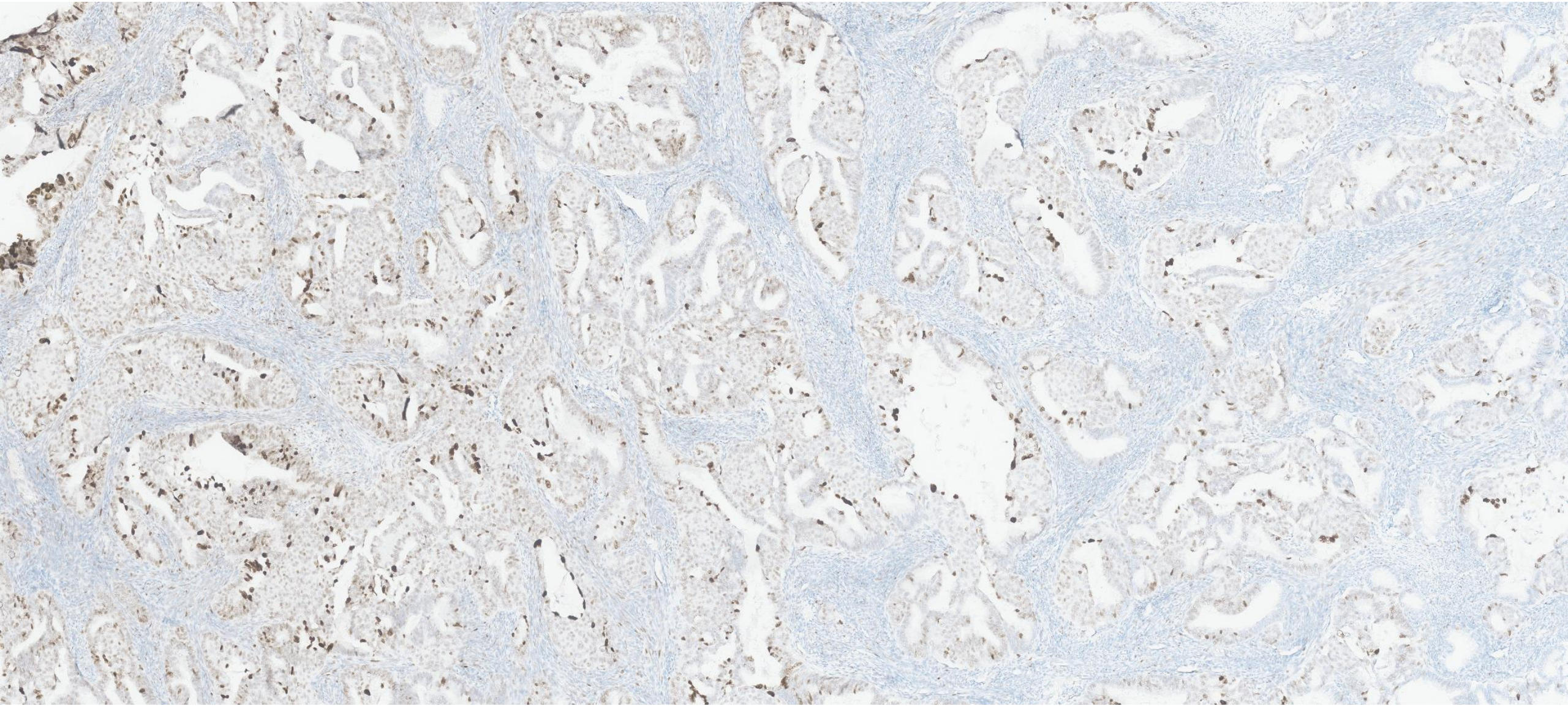


ER



PR

P53



Surgical pathology diagnosis

- Endometrial carcinoma, consistent with FIGO grade 2 endometrioid carcinoma (ER+, PR+, and p53 wild-type)
- Carcinoma shows myometrial invasion (<50%), no LVSI; other parts are negative
- The preliminary 2023 FIGO stage is IA, pending molecular classification.

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RESULT

The results provided within this report represent molecular testing results only. Please refer to the Surgical Pathology report for the integrated molecular and pathology diagnosis (if applicable).

Provided diagnosis: endometrial adenocarcinoma

Microsatellite Instability (MSI) status: Stable (MSS)

The following CLINICALLY RELEVANT VARIANTS were detected:

Gene: CTNNB1

DNA Change: c.110C>T (exon 3)

Amino Acid Change: p.S37F (Ser37Phe)

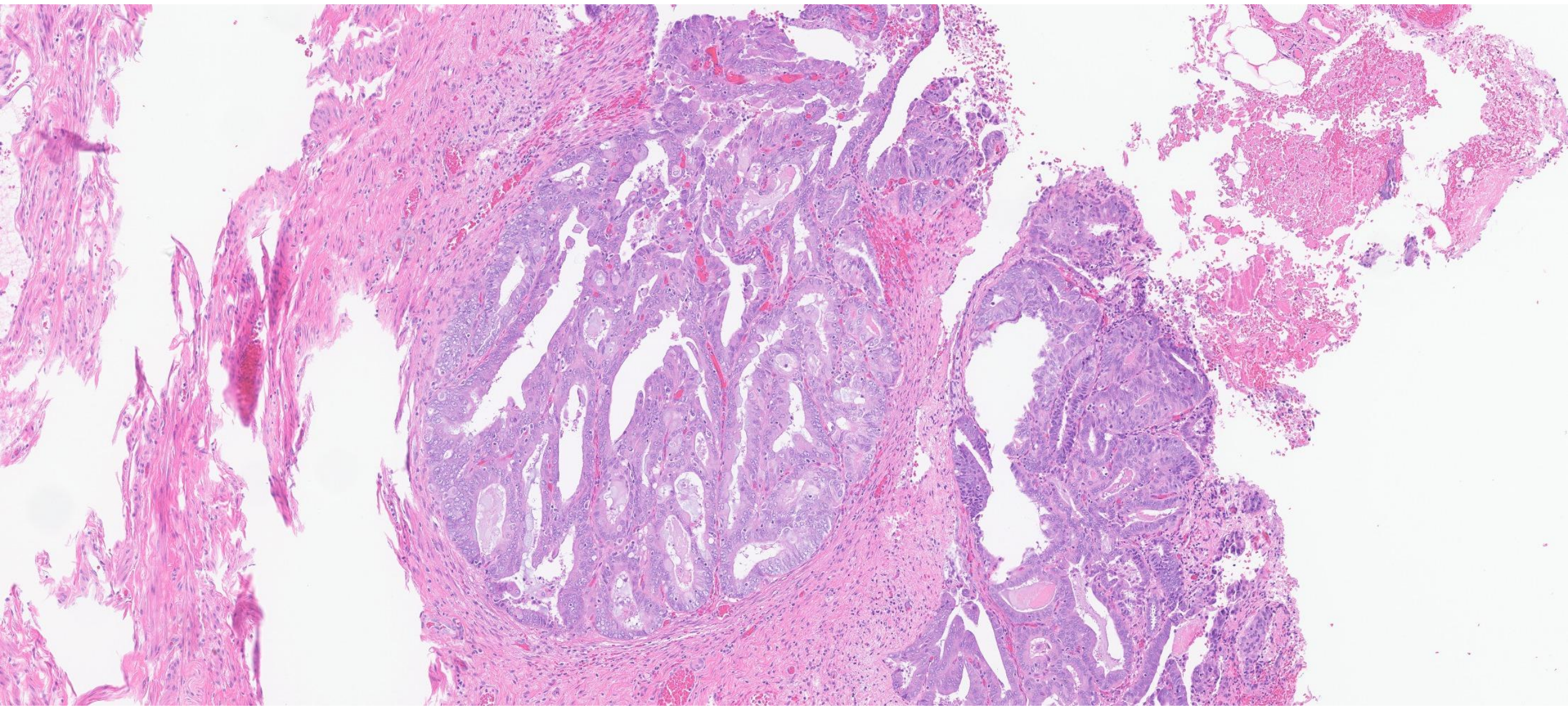
Variant Allele Frequency: 29.4%

Gene: TP53

DNA Change: c.848G>A (exon 8)

Amino Acid Change: p.R283H (Arg283His)

Variant Allele Frequency: 51.4%



Final surgical pathology diagnosis

- Endometrioid adenocarcinoma with p53 mutation
- Carcinoma involves right adnexal tissue
- 2023 FIGO stage is IIIA1.

Prognostic Risk Groups with MC

Risk Group	Molecular Classification Known
Low	• Stage I-II POLEmut endometrial carcinomas • IA MMRd/NSMP low grade endometrioid + focal or no LVSI
Intermediate	• IA MMRd/NSMP endometrioid + high grade + LVSI (- or focal) • IA p53abn without myometrial invasion • IB MMRd/NSMP endometrioid + low grade + -/focal LVSI
High-Intermediate	• I MMRd/NSMP endometrioid + extensive LVSI • IB MMRd/NSMP endometrioid + high grade regardless of LVSI • Stage II MMRd/NSMP endometrioid carcinoma
High	• Stage III-IVA MMRd/NSMP endometrioid carcinoma • Stage I-IVA p53abn + myometrial invasion • Stage III –IVA MMRd/NSMP other high grade carcinomas

Summaries

- **MC of EC is still a rapid changing field.**
- **If your institution is ready, do MC on all EC cases**
- **If not**, use IHC markers you already have, such as p53, ER/PR, MMR on all cases and select cases need to be sent out for MC
- Gross examination and sampling of the TAH-BSO specimen is **STILL** important
- Integrated molecular diagnosis with morphology and the 2023 FIGO staging, do communicate clearly with your clinicians.

We are part of the team and play a critical role!

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Gynecologic Oncology

Endometrial Cancer: Who Lives, Who Dies, Can We Improve Their Story?

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Endometrial cancer • Mismatch repair defect • Immunotherapy • Cancer death • Mortality

Thank you!

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