Immunohistochemistry and molecular testing in endometrial carcinoma

Naveena Singh

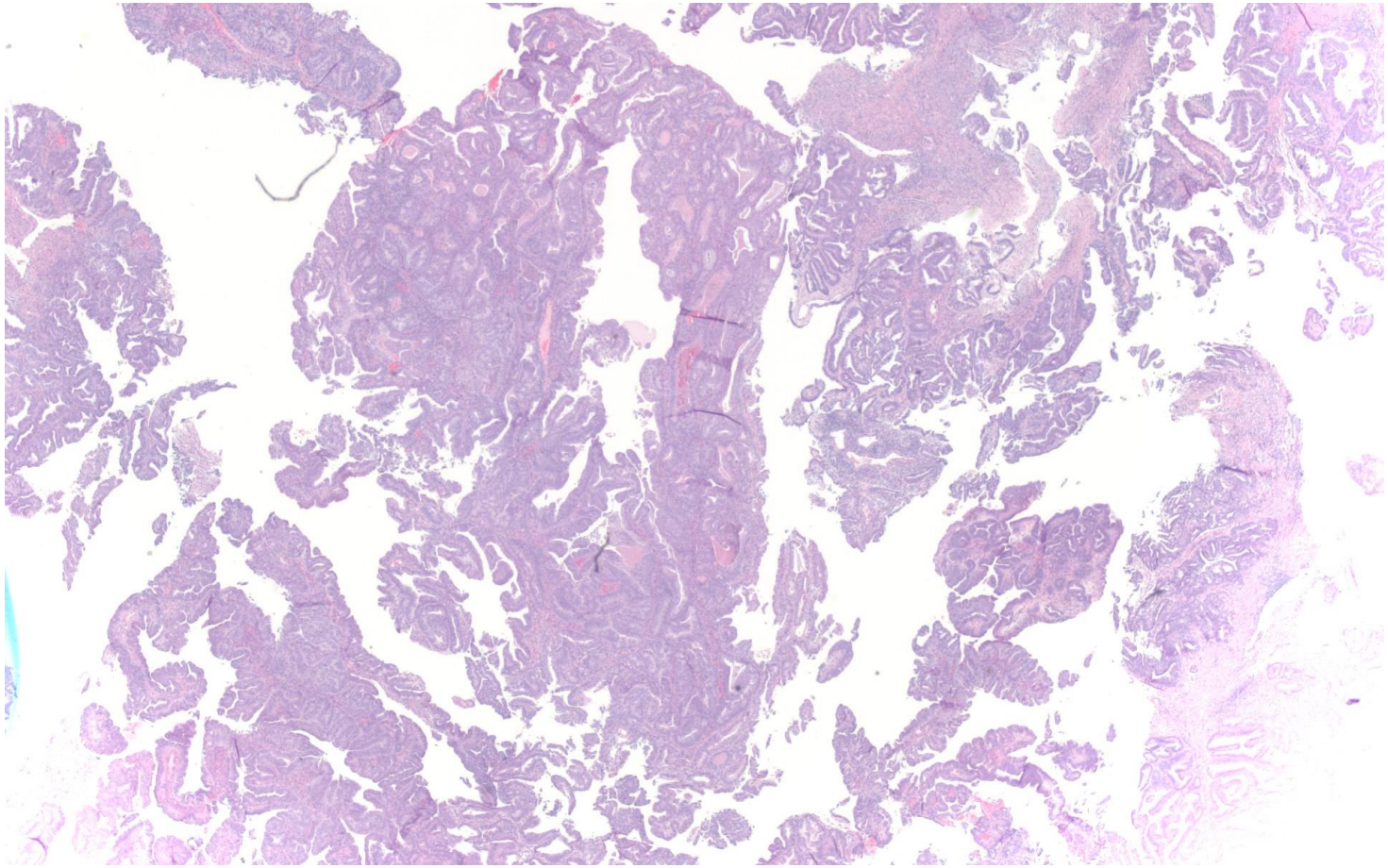
Vancouver General Hospital and the University of British Columbia

(Barts Health NHS Trust and Queen Mary University of London)

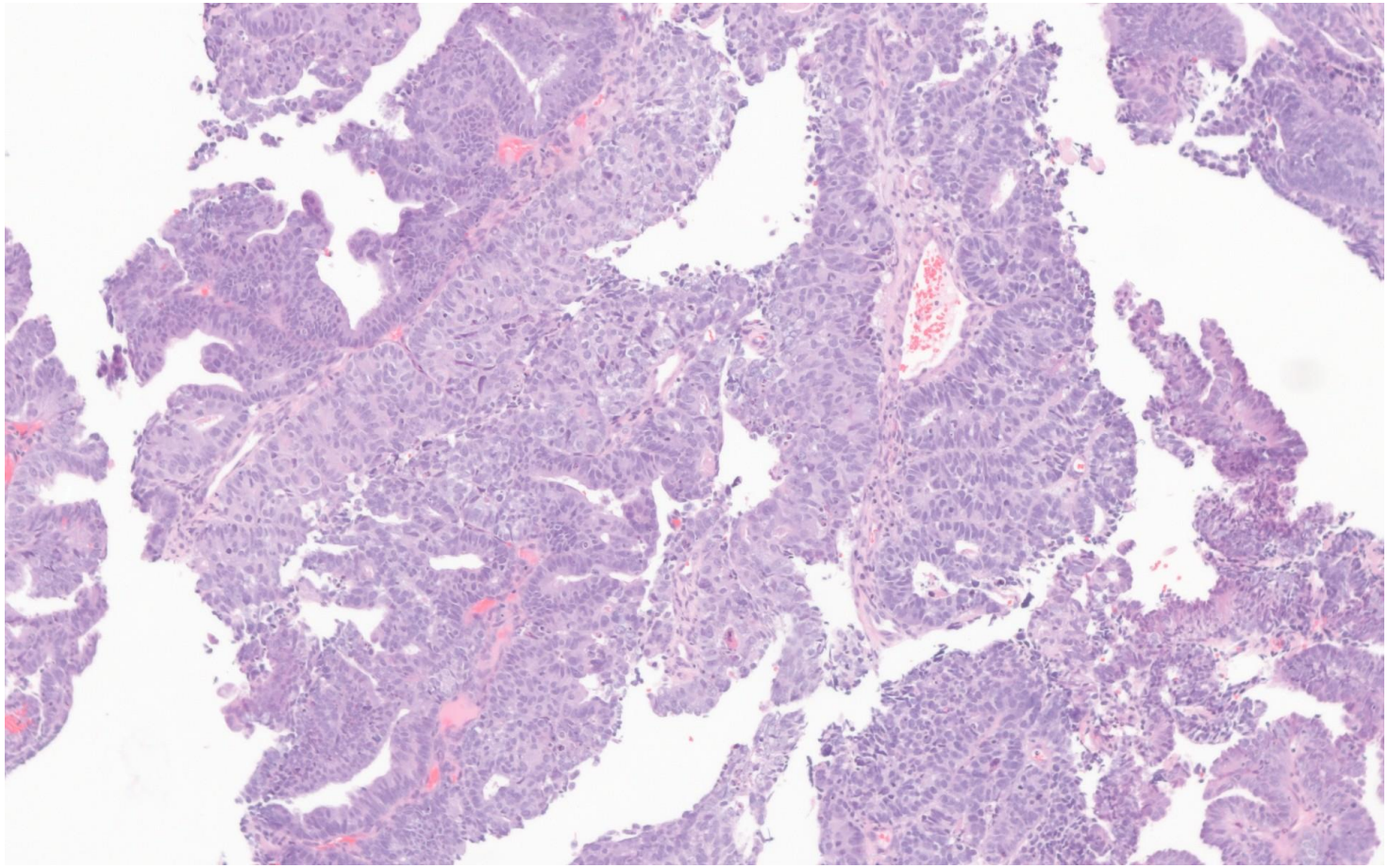
Case 1:

- 56F
- 1 year h/o vaginal bleeding, thought to be perimenopausal but sought medical attention when it led to chronic fatigue
- Pelvic USS: Thickened endometrium, biopsied

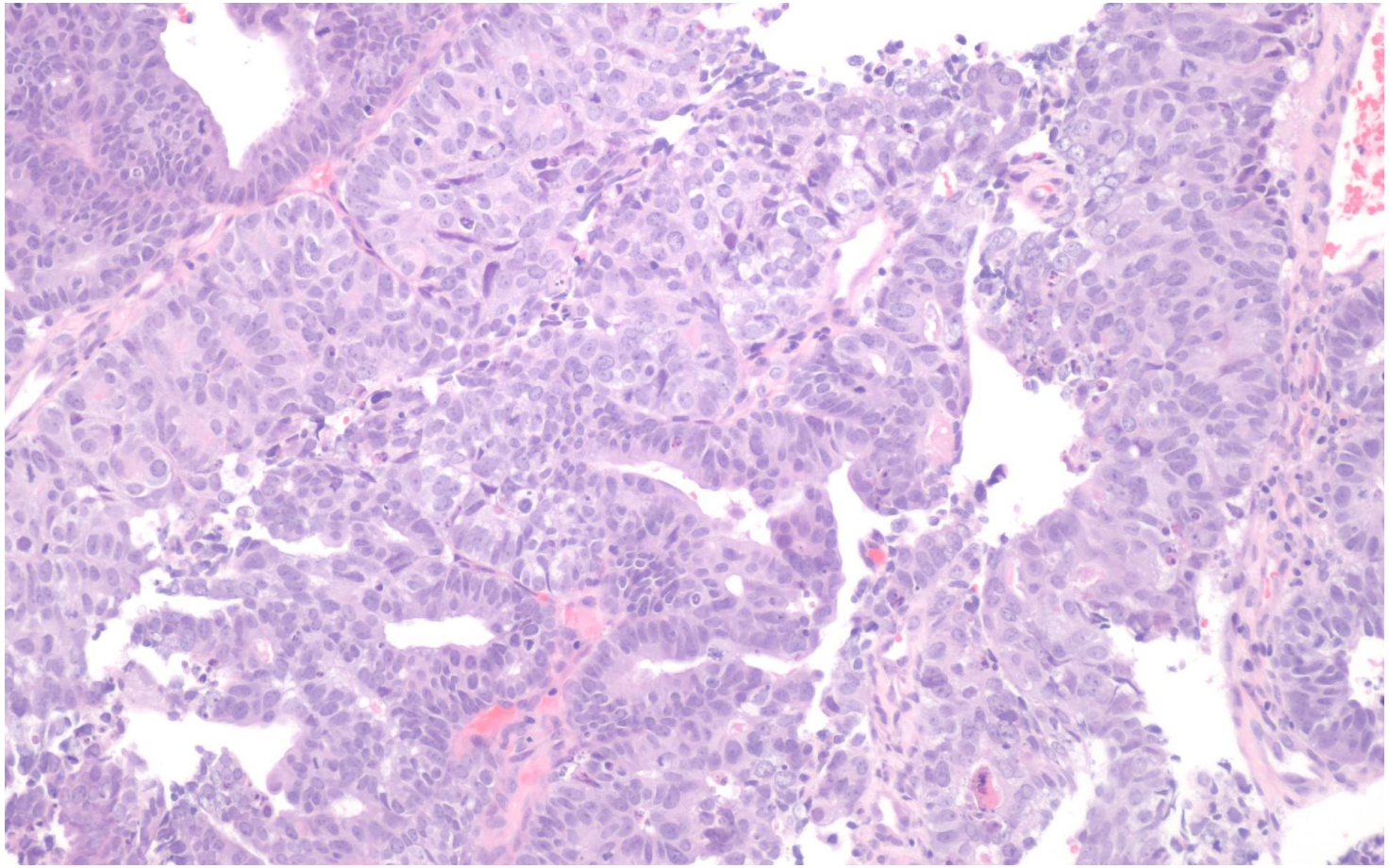
Case 1: Biopsy



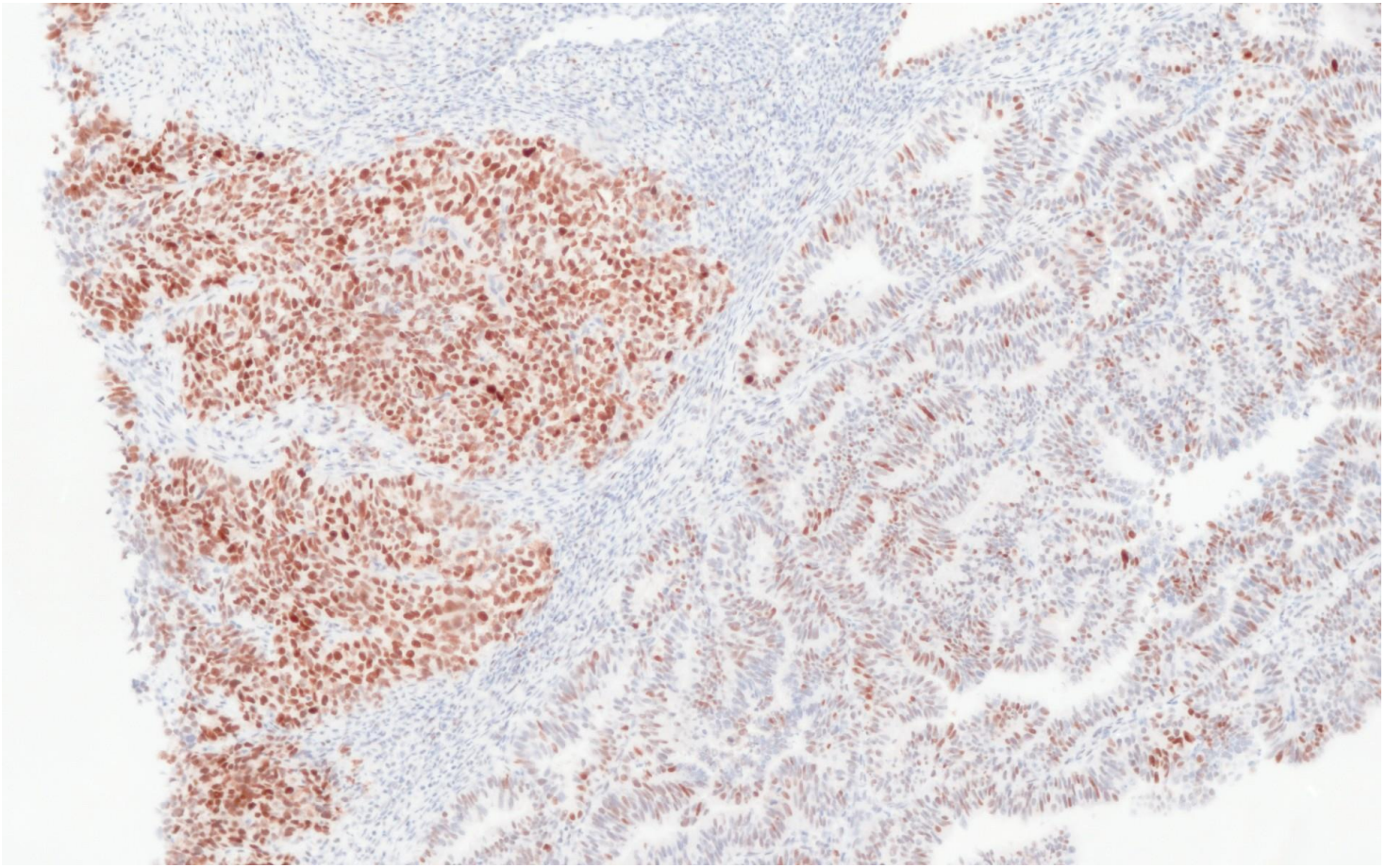
Case 1: Biopsy



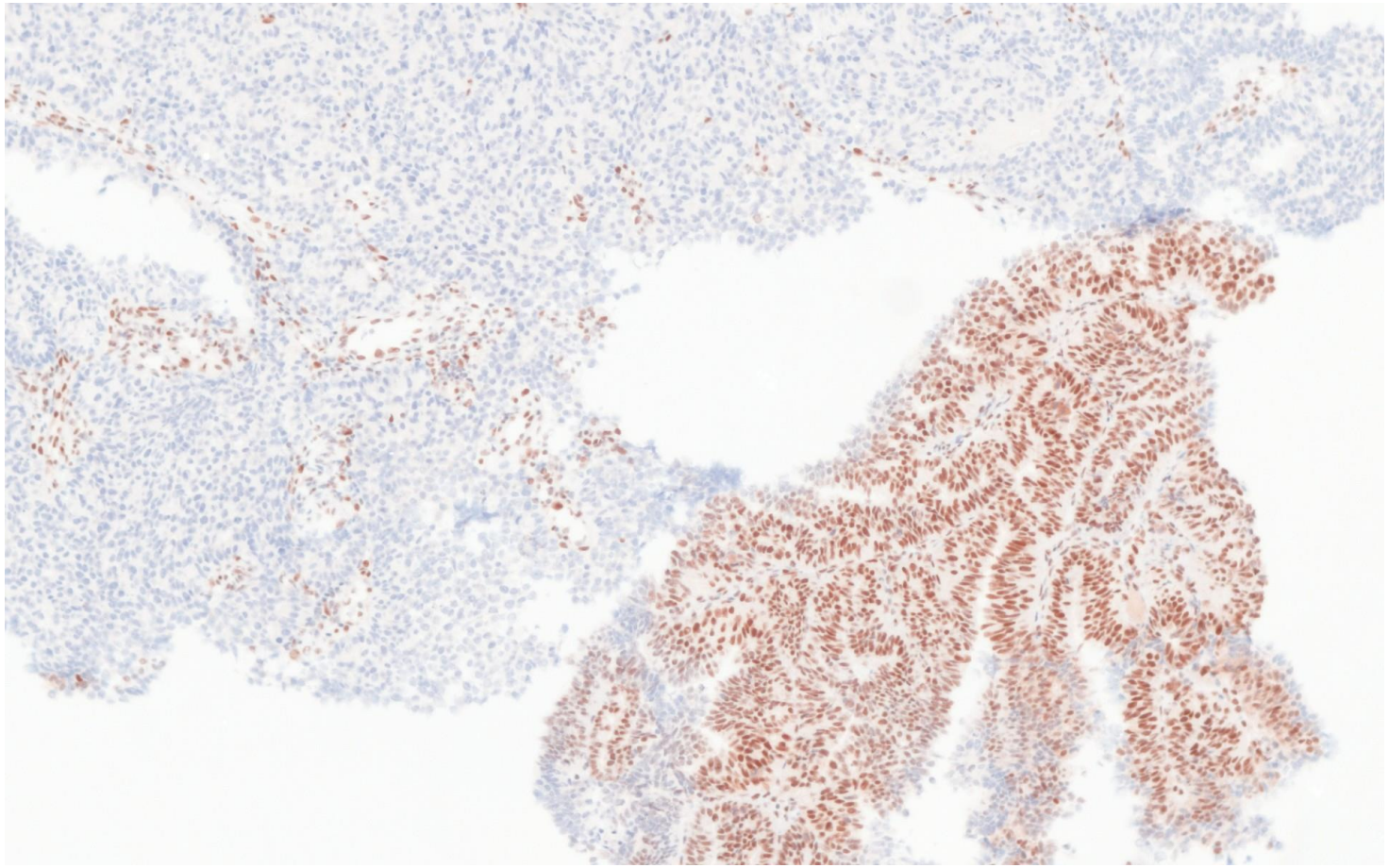
Case 1: Biopsy



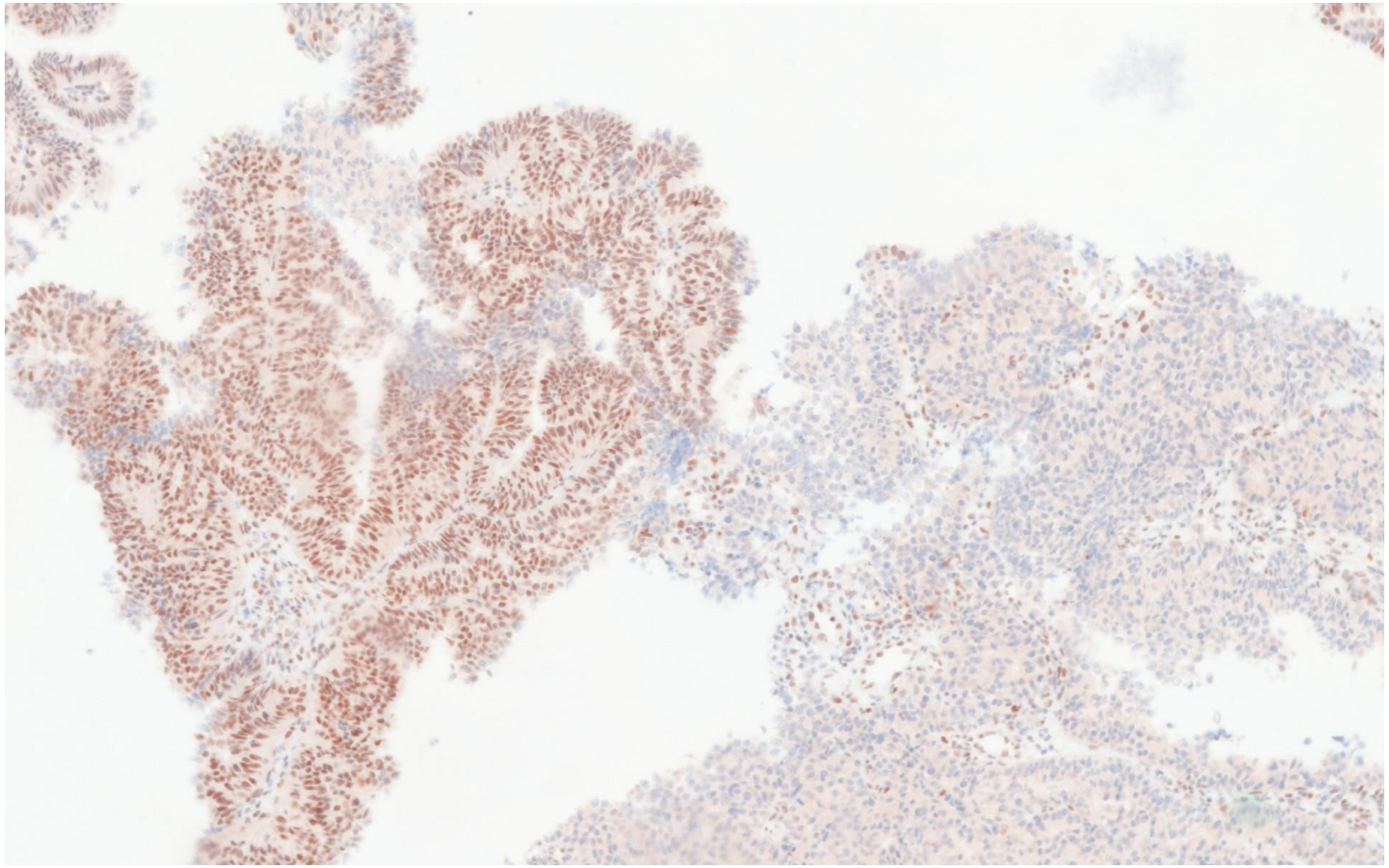
Subclonal p53 IHC



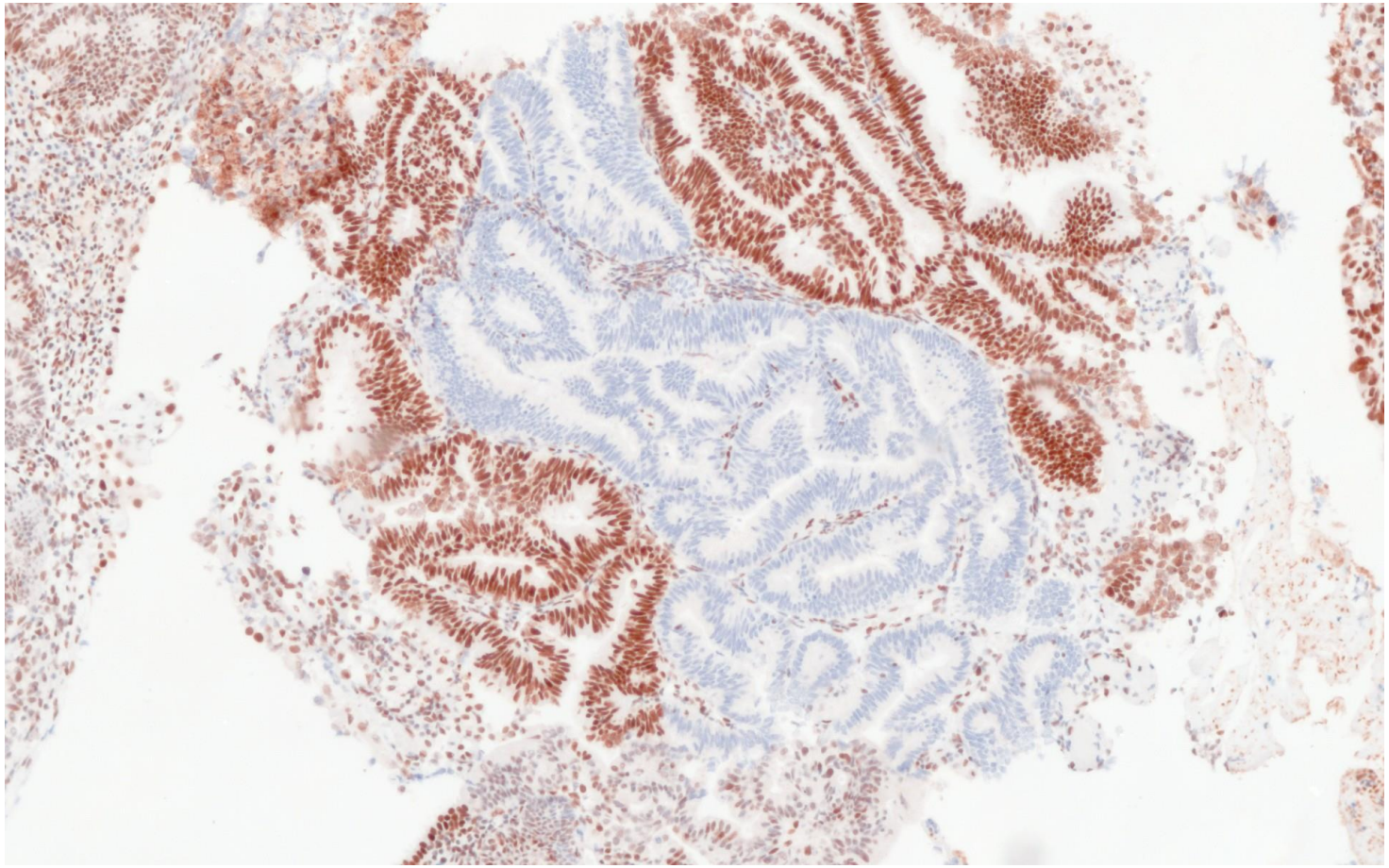
Subclonal MMR IHC: MLH1



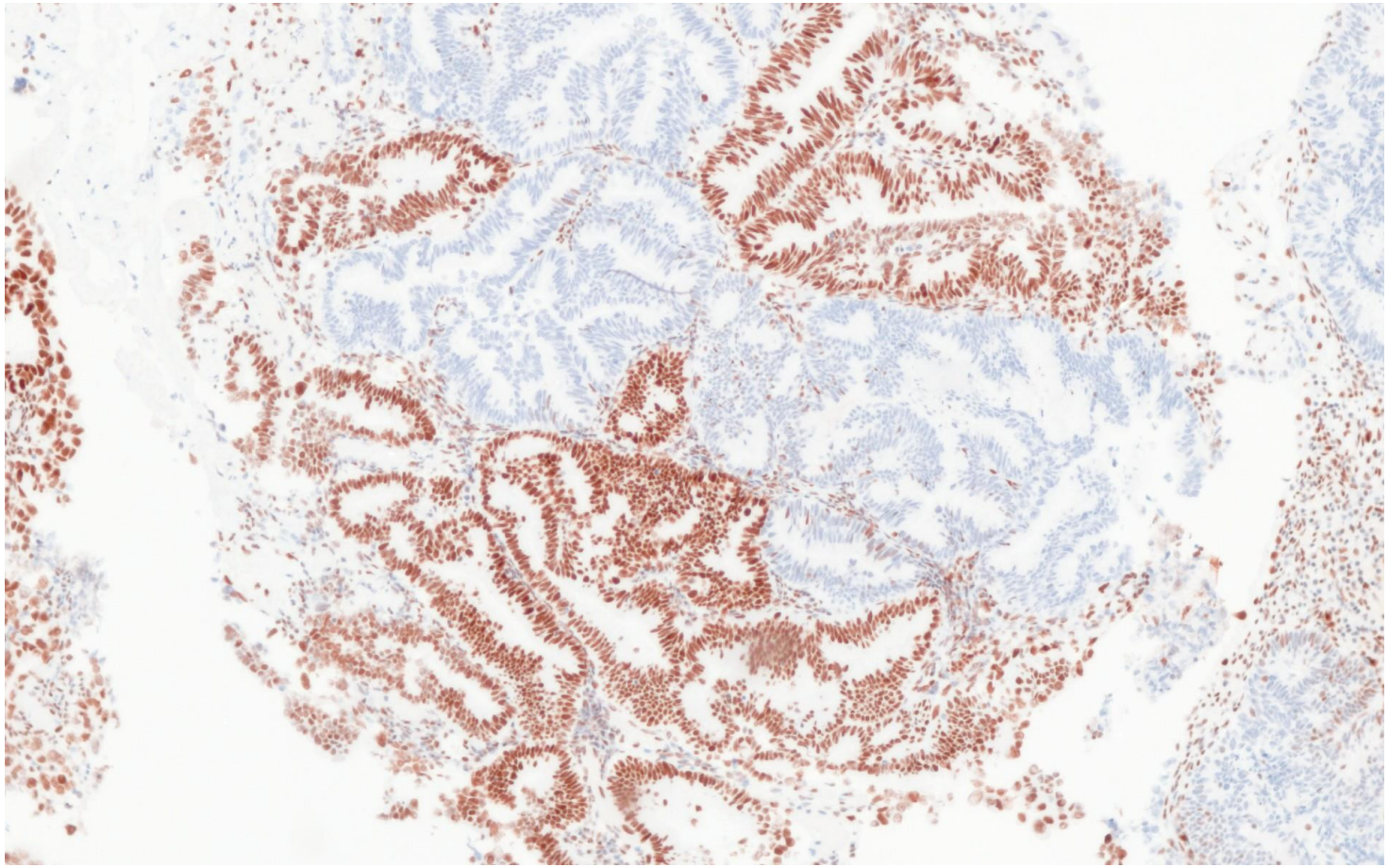
Subclonal MMR IHC: PMS2



Subclonal MMR IHC: MSH2



Subclonal MMR IHC: MSH6



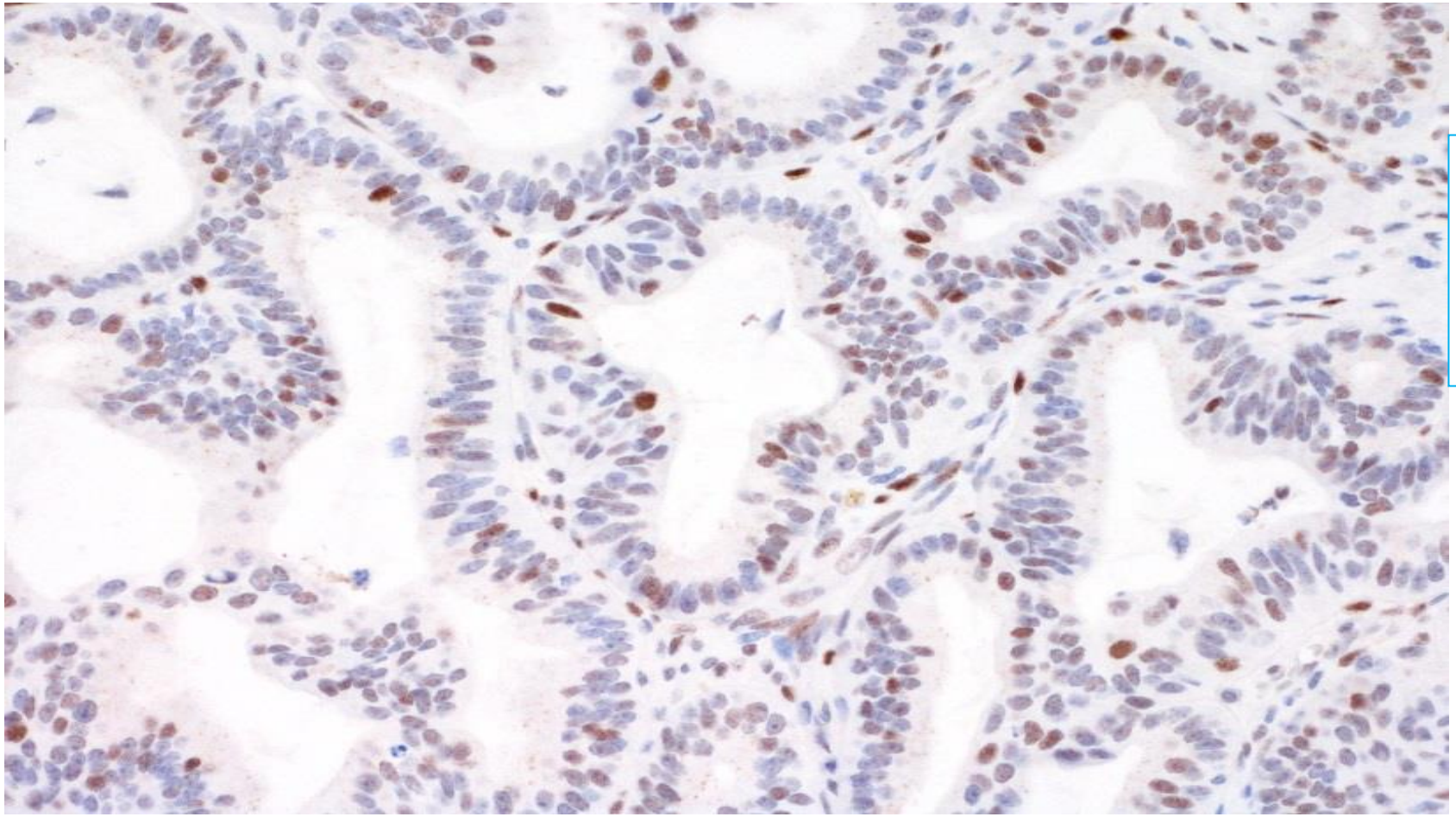
Case 1: Biopsy report

- High-grade adenocarcinoma with subclonal MMR loss as well as subclonal p53 expression

- *POLE* testing requested.

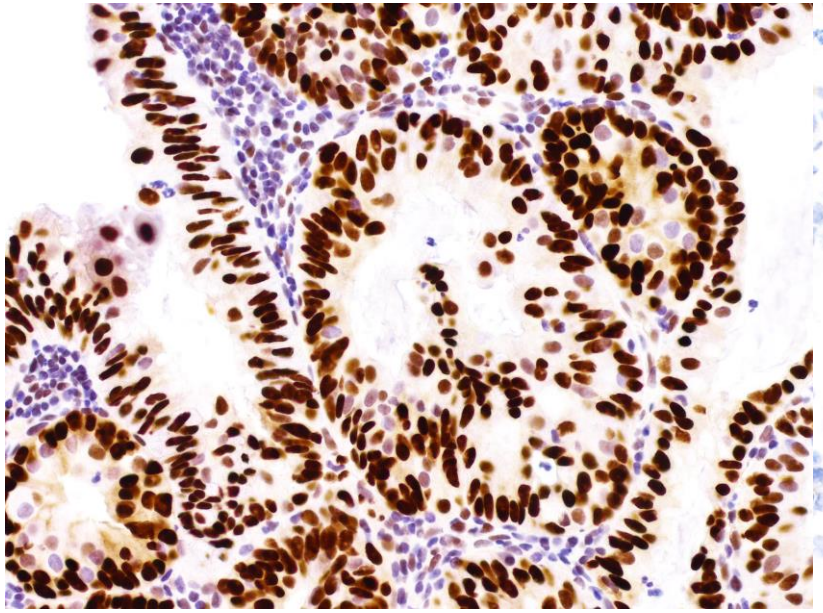
Interpretation of p53 immunohistochemistry

No *TP53* mutation

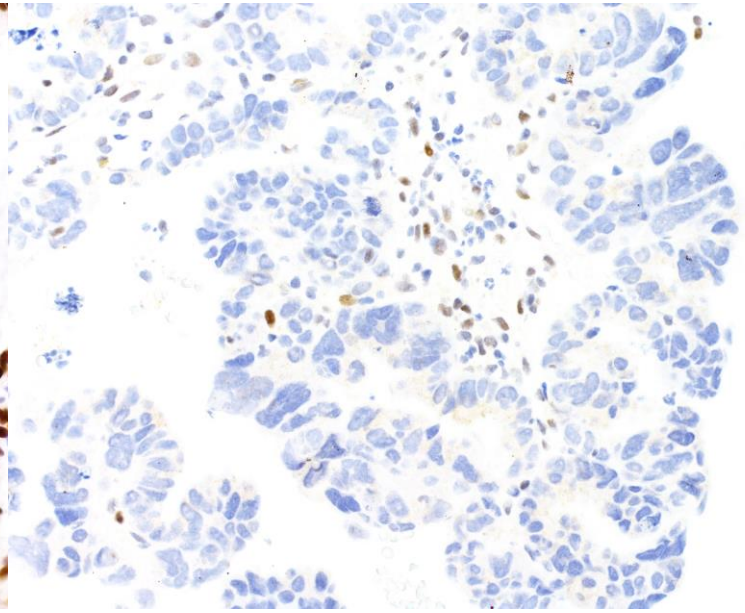


Normal or ‘wild-type’ pattern

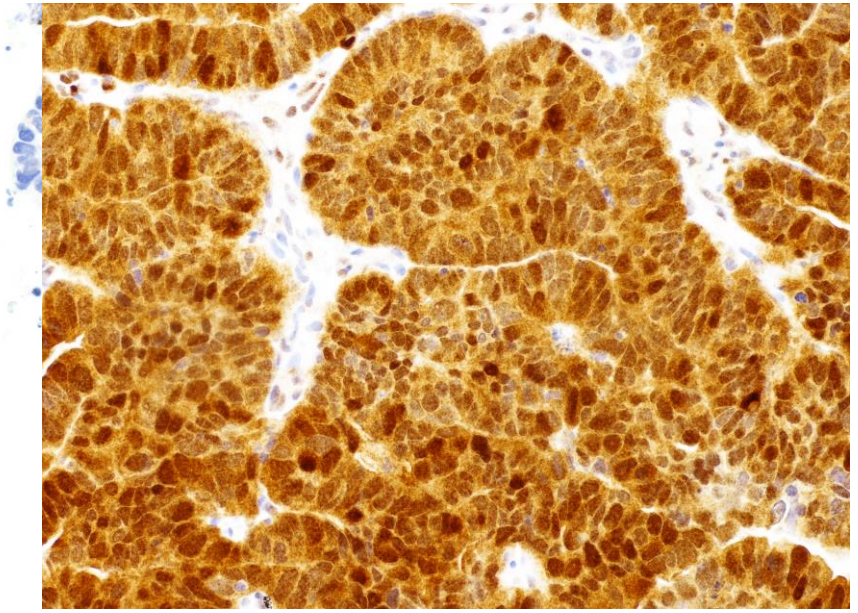
p53 IHC in endometrial ca: 3 patterns of abnormal expression



Over-expression

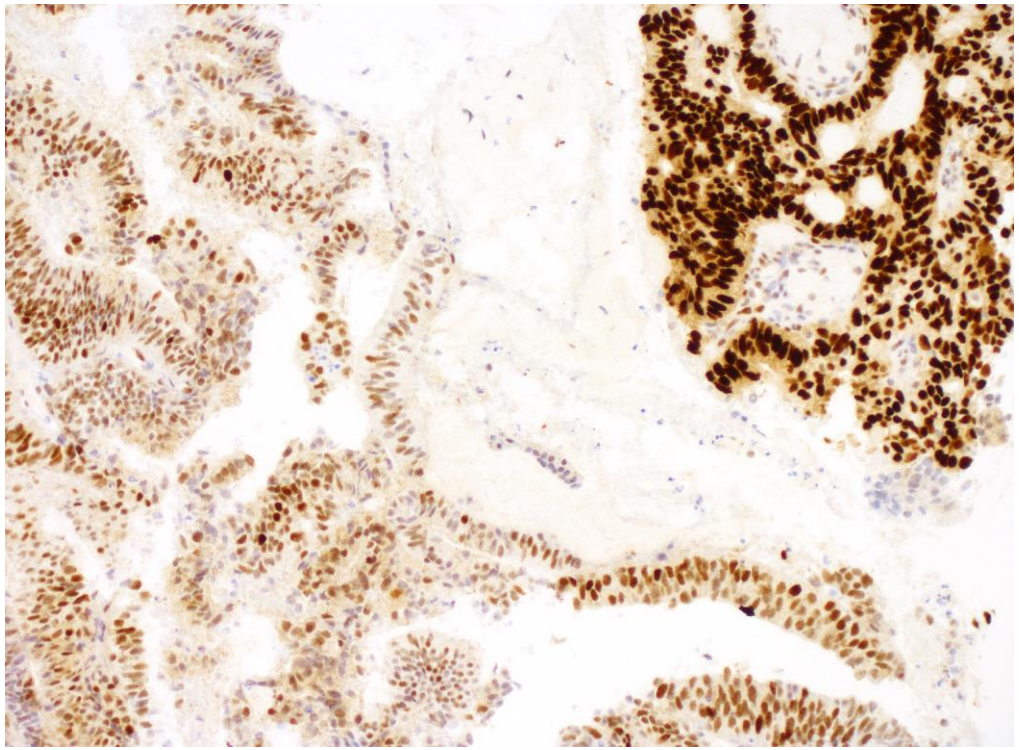


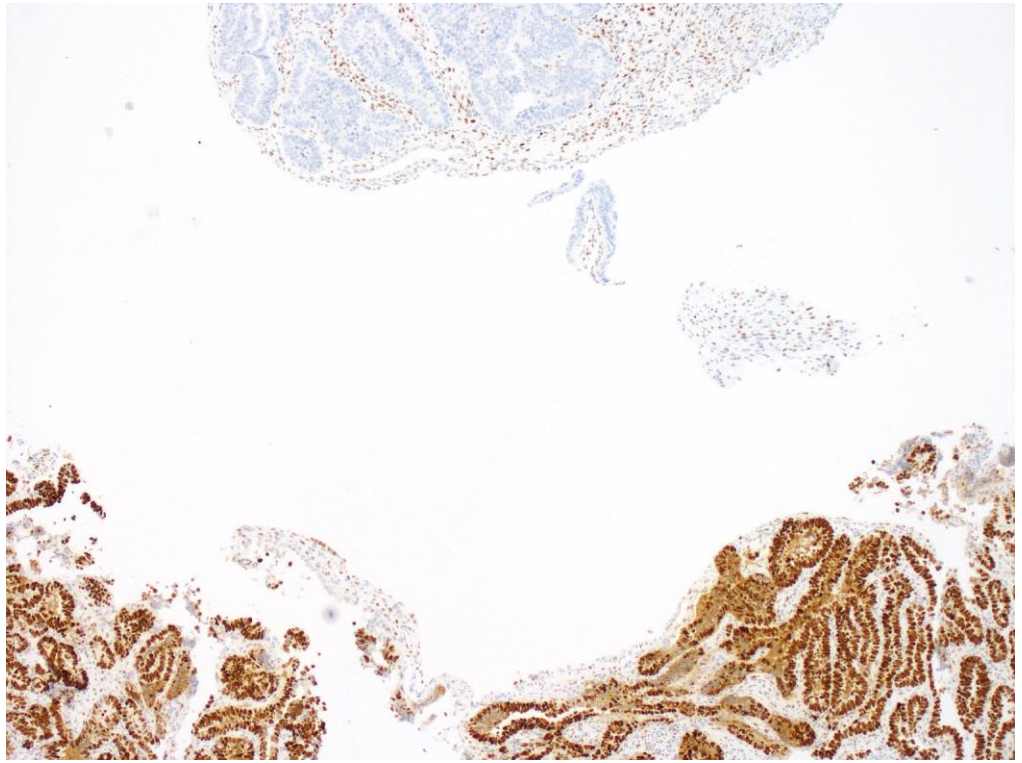
Complete absence



Cytoplasmic

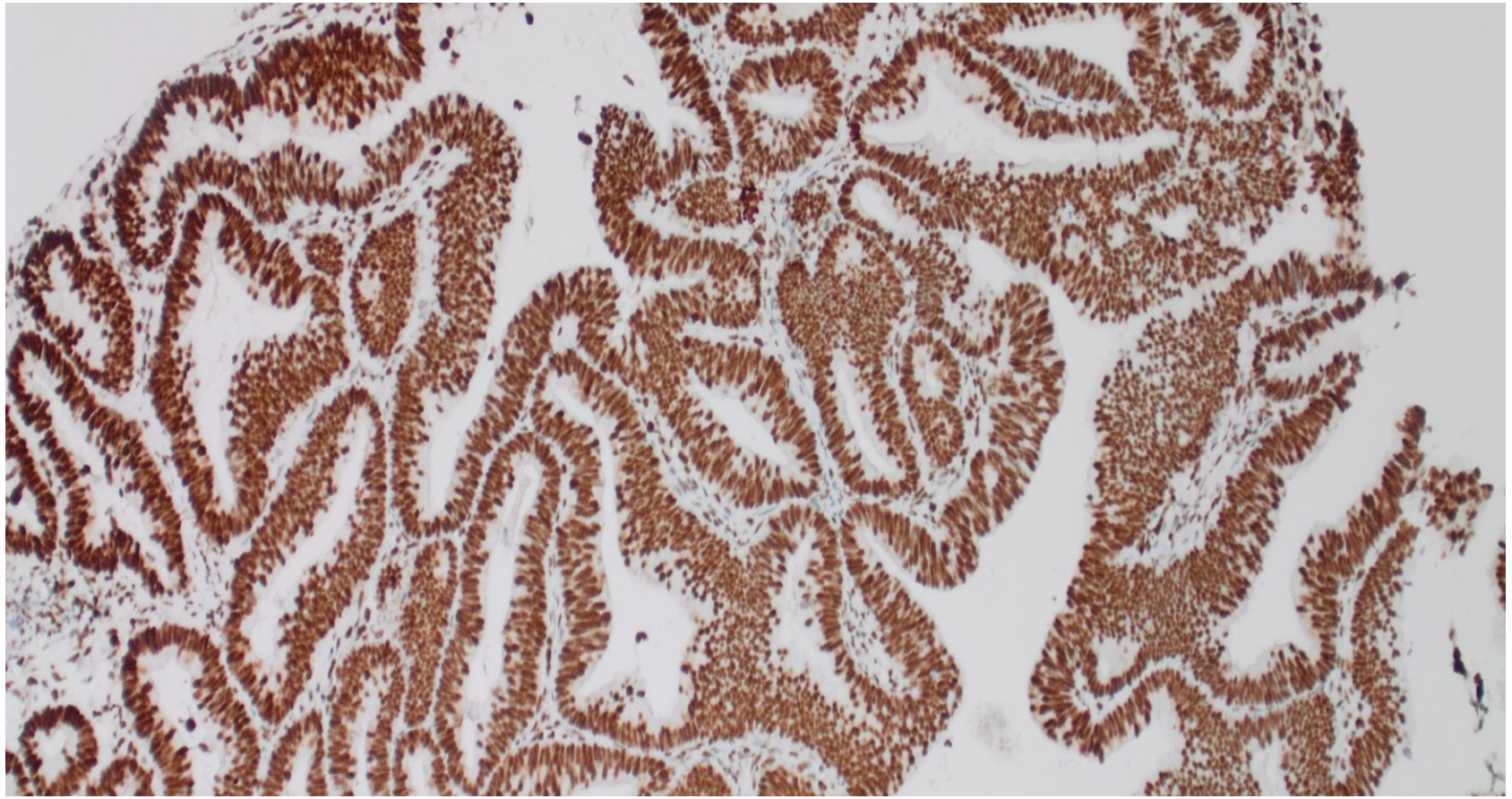
p53 IHC in endometrial ca: Subclonal expression; most often in MMRd/POLEmut EC



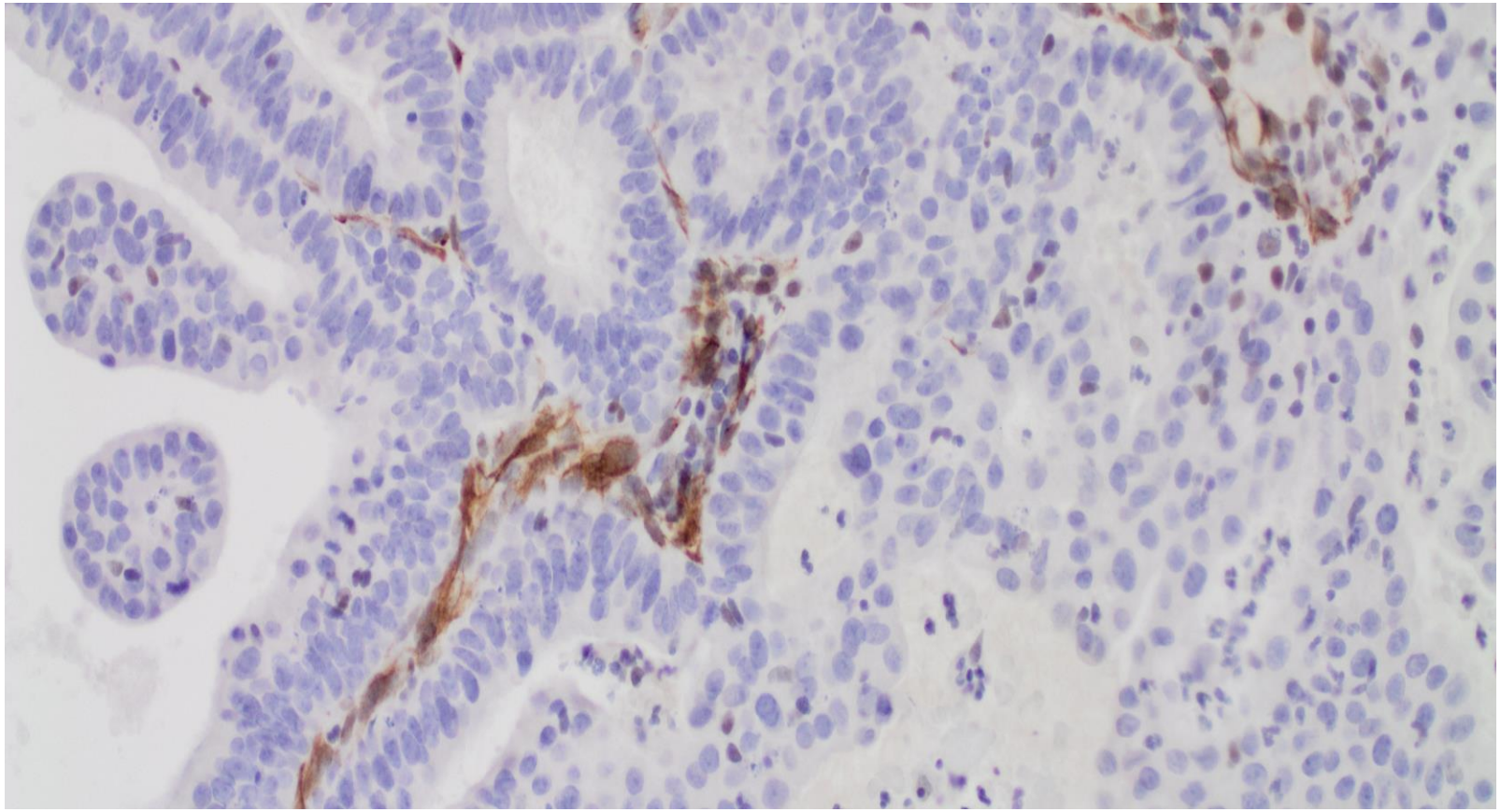


Interpretation of MMR IHC

MMR IHC: Normal expression

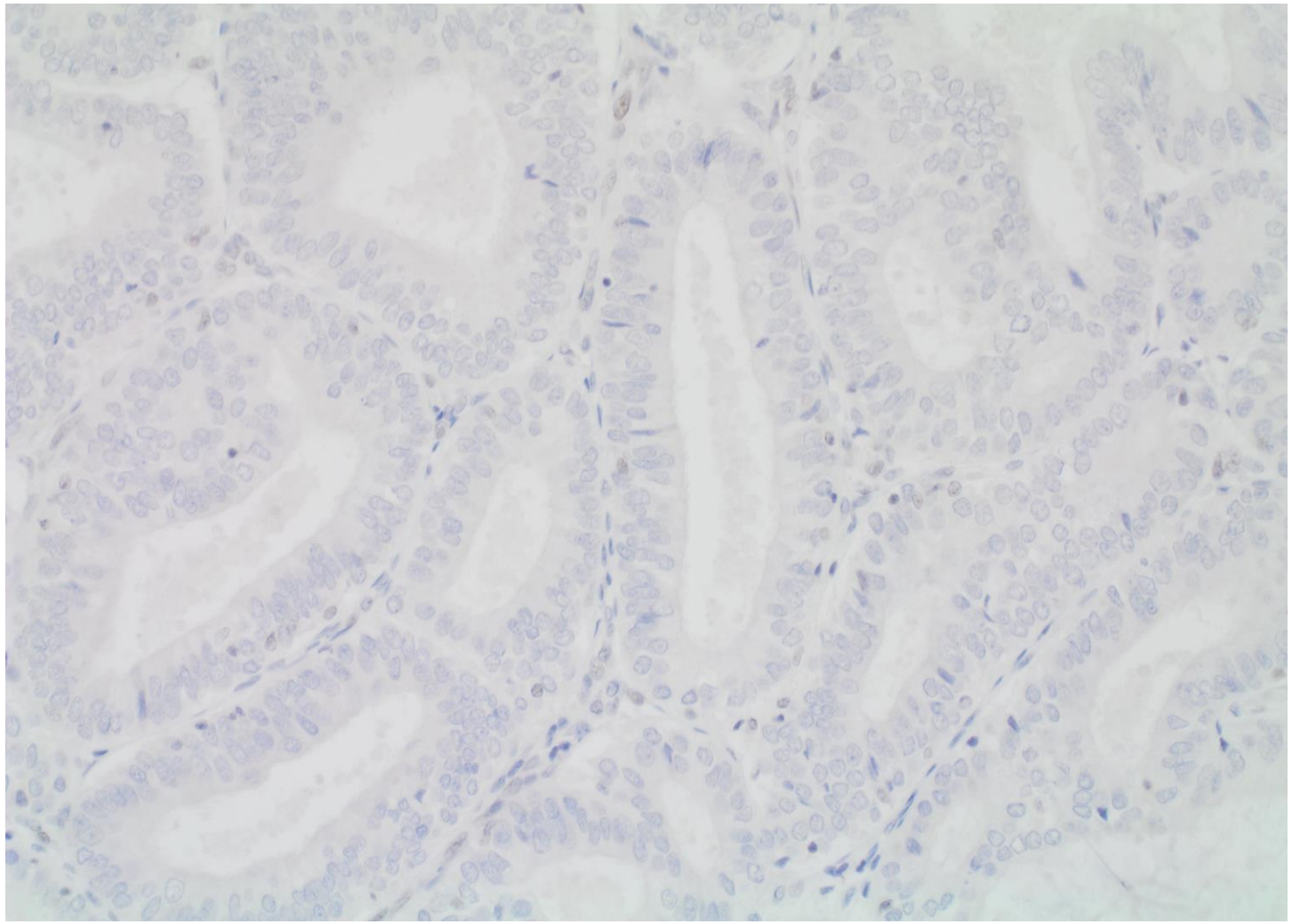


MMR IHC: Loss of expression



MMR IHC: Problems in interpretation

MMR IHC, Problems & pitfalls: POOR FIXATION

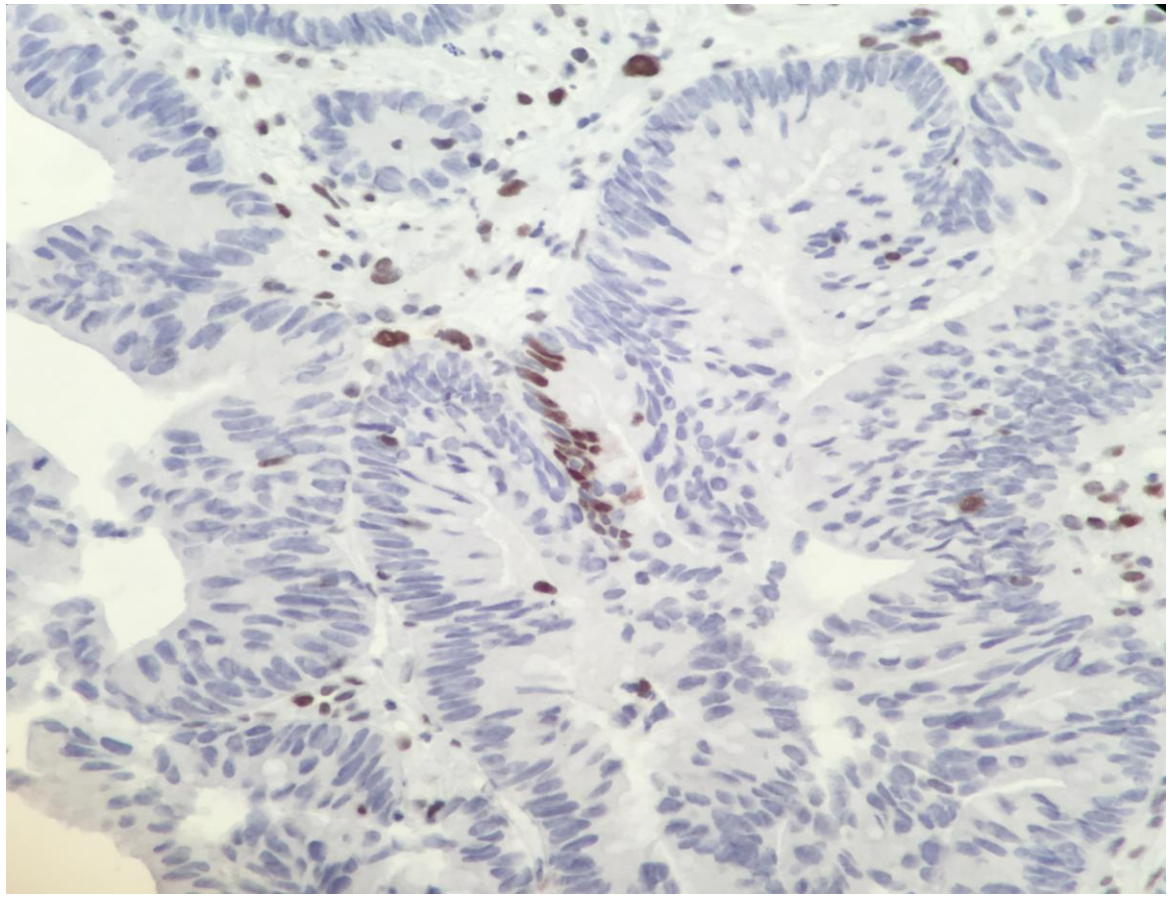


MMR IHC, Problems & pitfalls: POOR FIXATION

- **Fixation** affects IHC detection (use BIOPSIES)
- Staining protocol should be standardised with appropriate QC (external proficiency testing, eg UKNEQAS)
- Due regard to presence of internal control
- Other reasons for loss of expression: neoadjuvant chemo; freezing of tissue

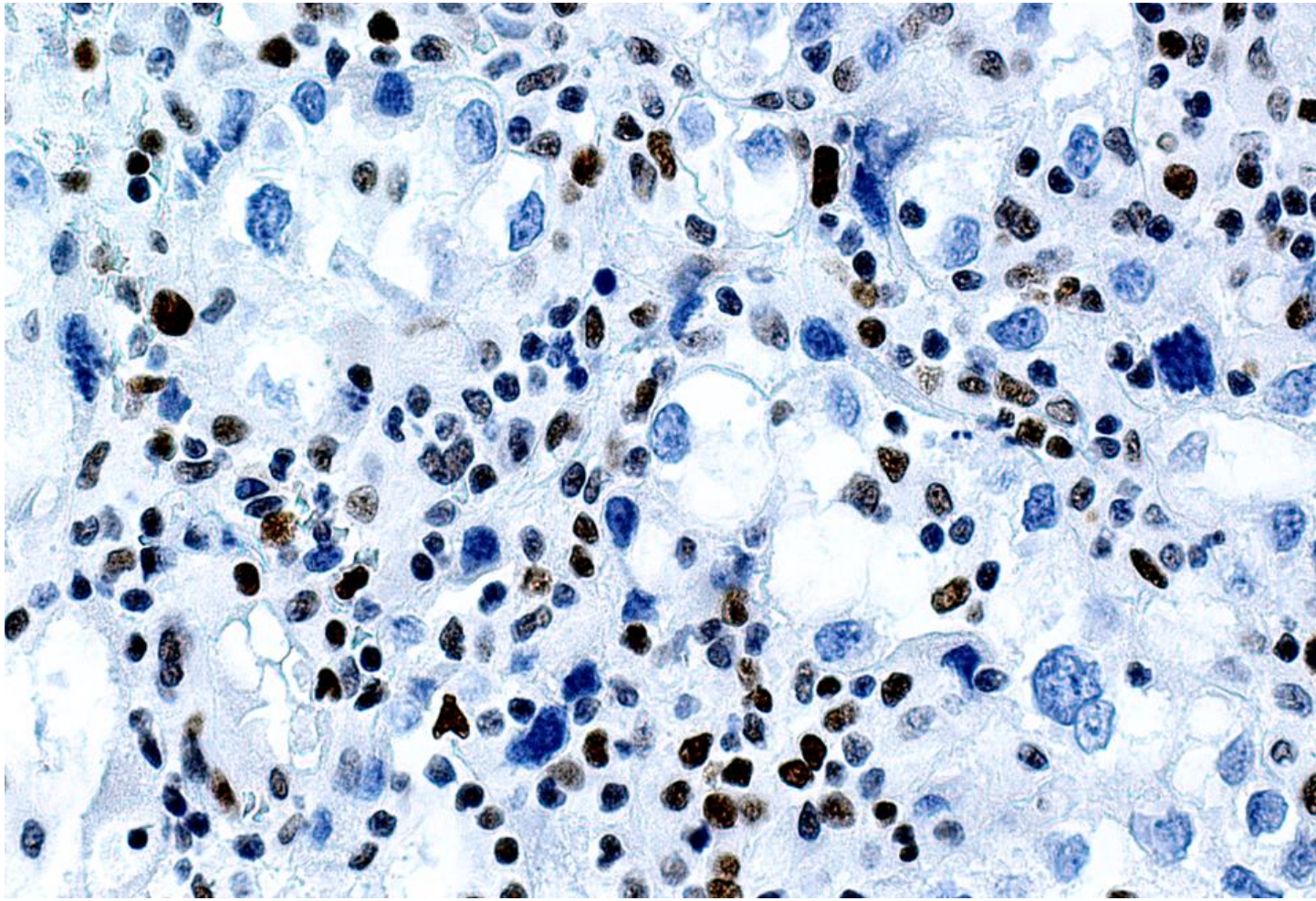
MMR IHC, Problems & pitfalls: WEAK/FOCAL EXPRESSION

- Standard teaching: ‘any positivity’ is reported as retained expression
- Some missense mutations can result in weak/focal expression
- Very weak staining/very focal expression (in comparison to internal control) best regarded as ‘loss’

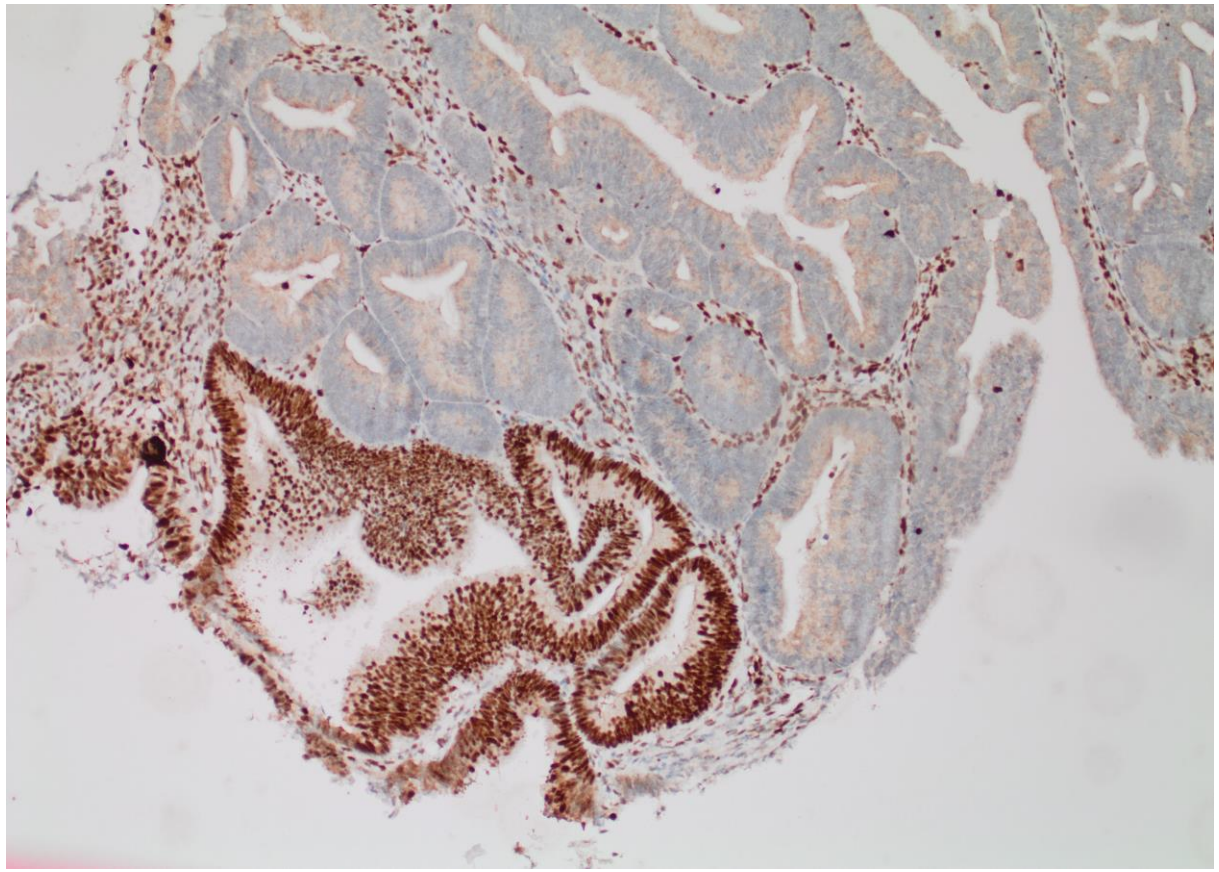


MMR IHC, Problems & pitfalls: Lymphocytes/stromal cells

- MMRd EC typically have large numbers of TIL's
- Do not interpret these or stromal cells as positive

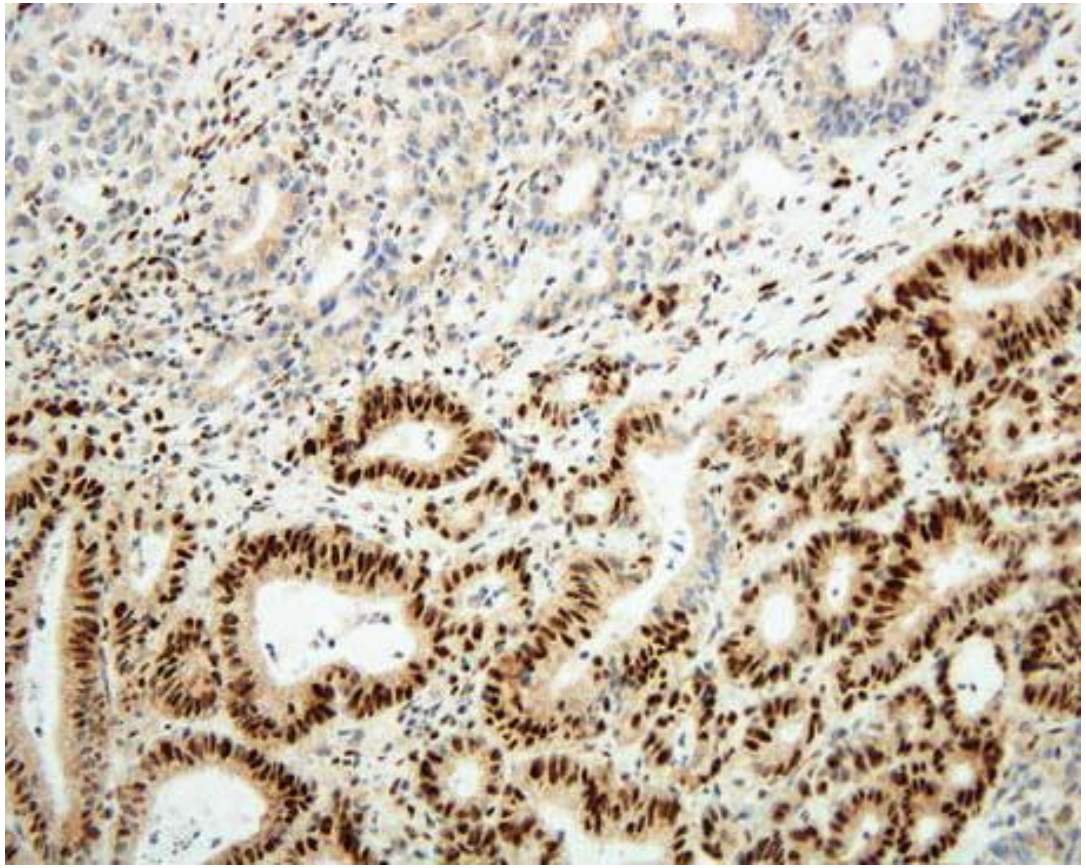


MMR IHC, Problems and pitfalls: HETEROGENEOUS loss (subclonal pattern)



- Exclude fixation artefact (internal control positive)
- Results from actual tumour heterogeneity as subclones with survival advantage are gradually propagated
- Most commonly seen with epigenetic MLH1 defect

MMR IHC, Problems and pitfalls: HETEROGENEOUS loss of MSH6



- MSH6 gene has a mutation-prone microsatellite: exon 5, polycytosine tract (C8); can undergo frame shift mutation in cases with MSI
- This can result in subclonal MSH6 loss in MSI due to ANY CAUSE – ie sporadic/germline
- Subclonal MSH6 loss therefore (almost always) indicates absence of MSH6 germline defect

Graham et al, AJSP 2015; 39:1370

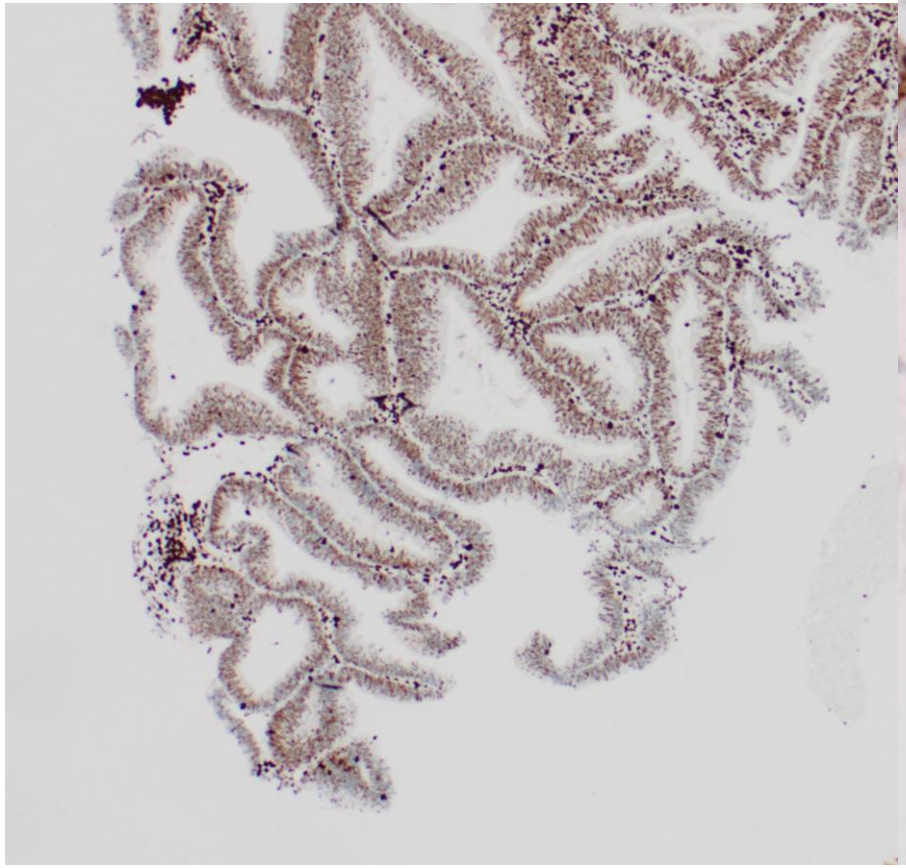
MMR IHC, Problems and pitfalls: HETEROGENEOUS patterns recommendations

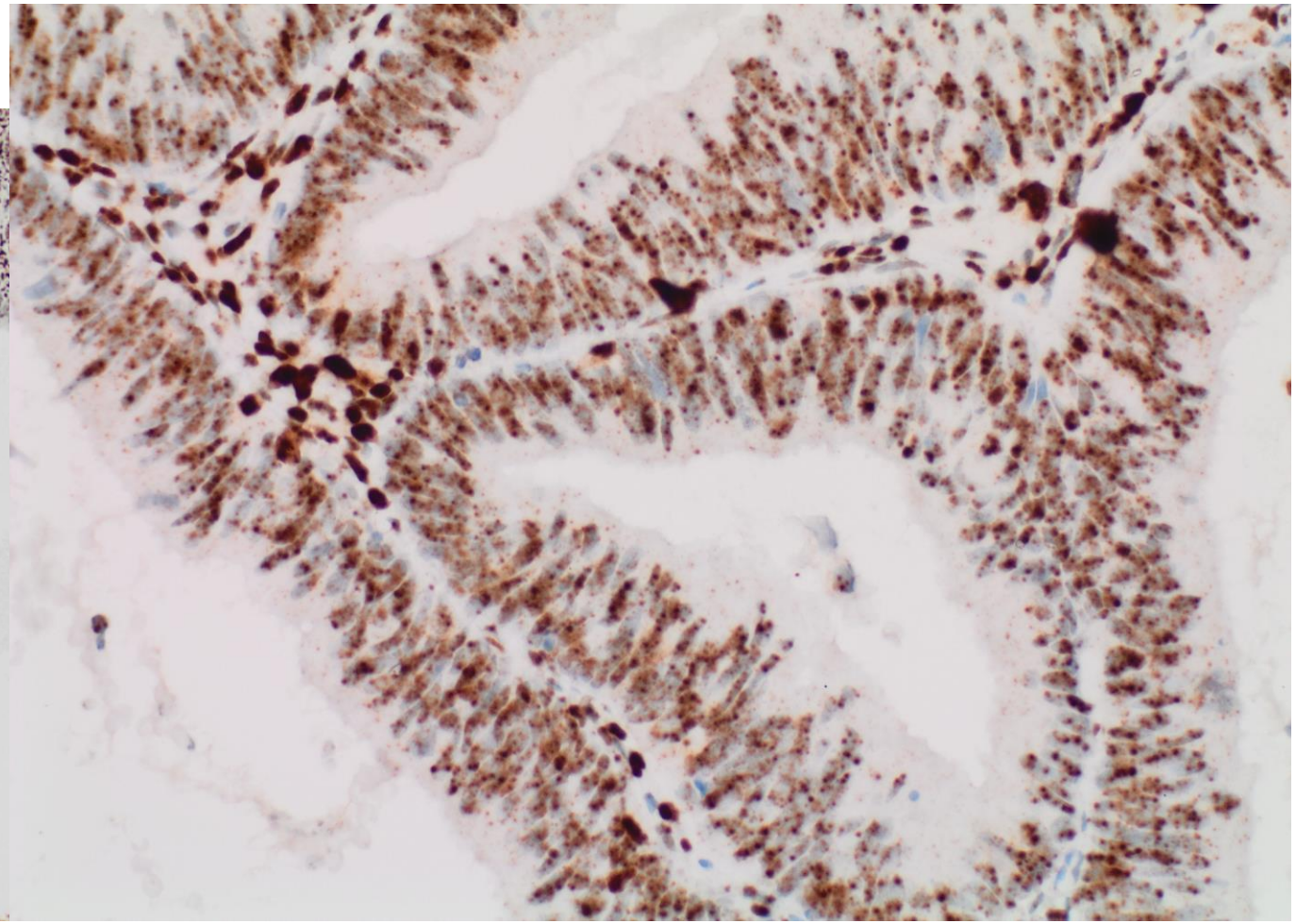
- 10% cut off has been suggested
- Some cases may represent germline defects
- Report as MMRd (subclonal MMR loss) as biology currently poorly understood

MMR IHC, Problems and pitfalls: FALSE NEGATIVE RESULT

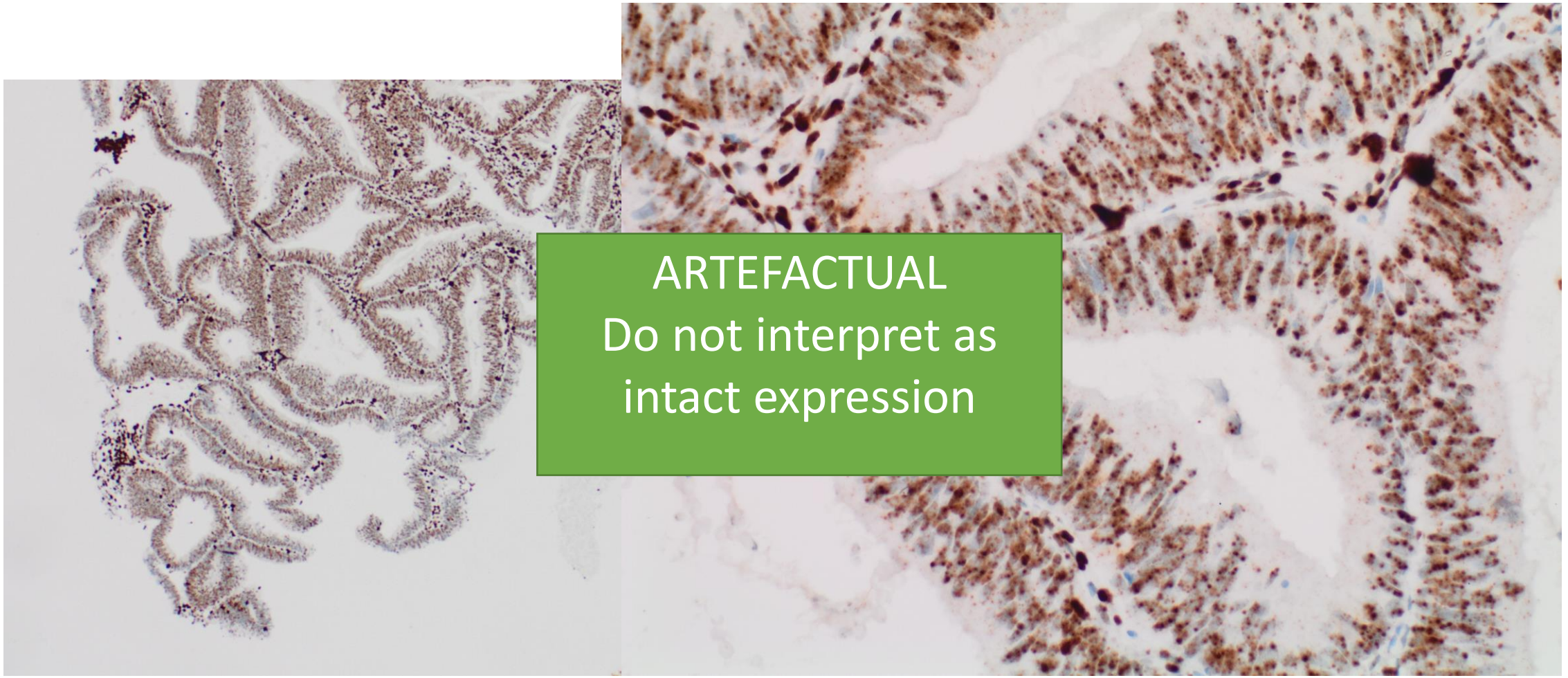
- Non-functional protein with retained antigenicity (most commonly MLH1)
- MSI +/- Germline testing if strong family history

MMR IHC, Problems and pitfalls: DOT-LIKE STAINING





MMR IHC, Problems and pitfalls: DOT-LIKE STAINING

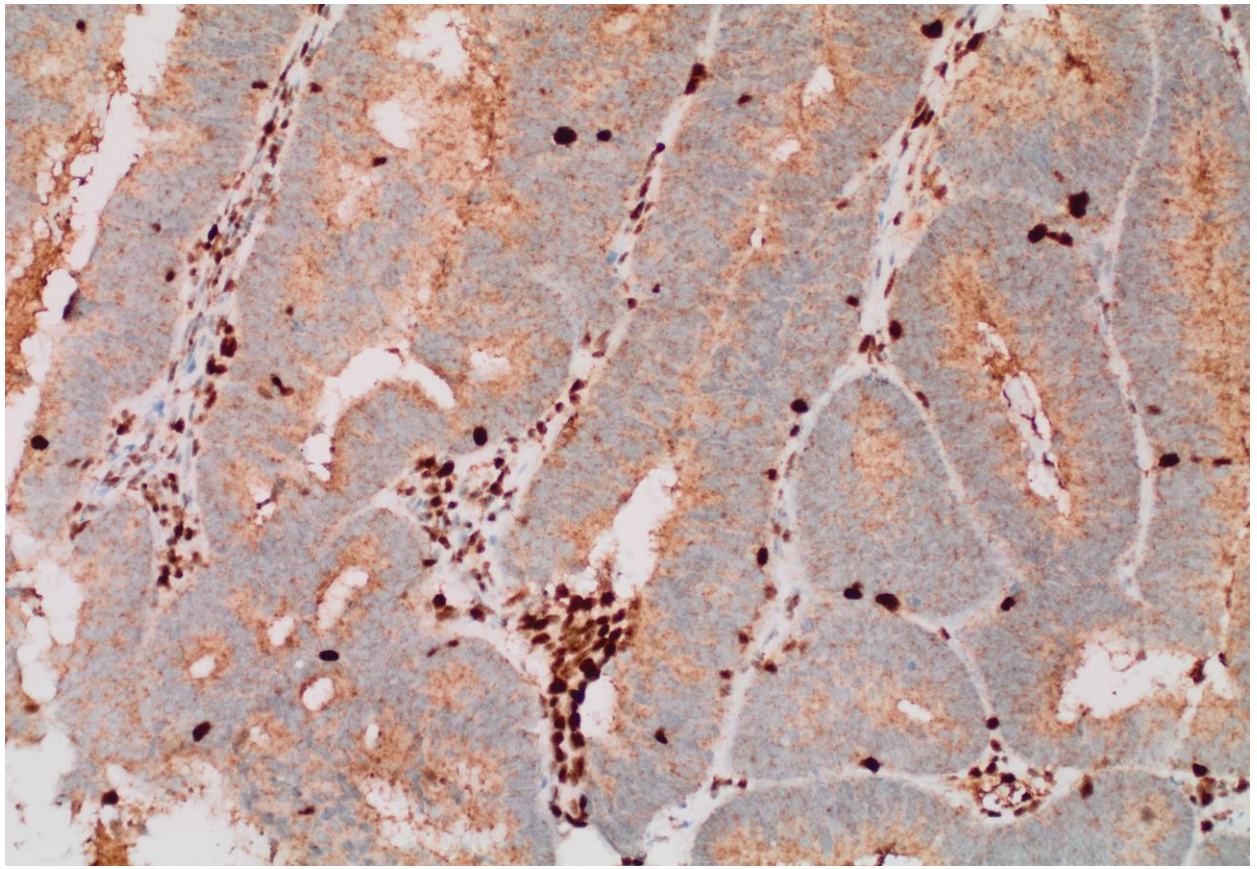


USCAP Platfrom presentation, March 2022

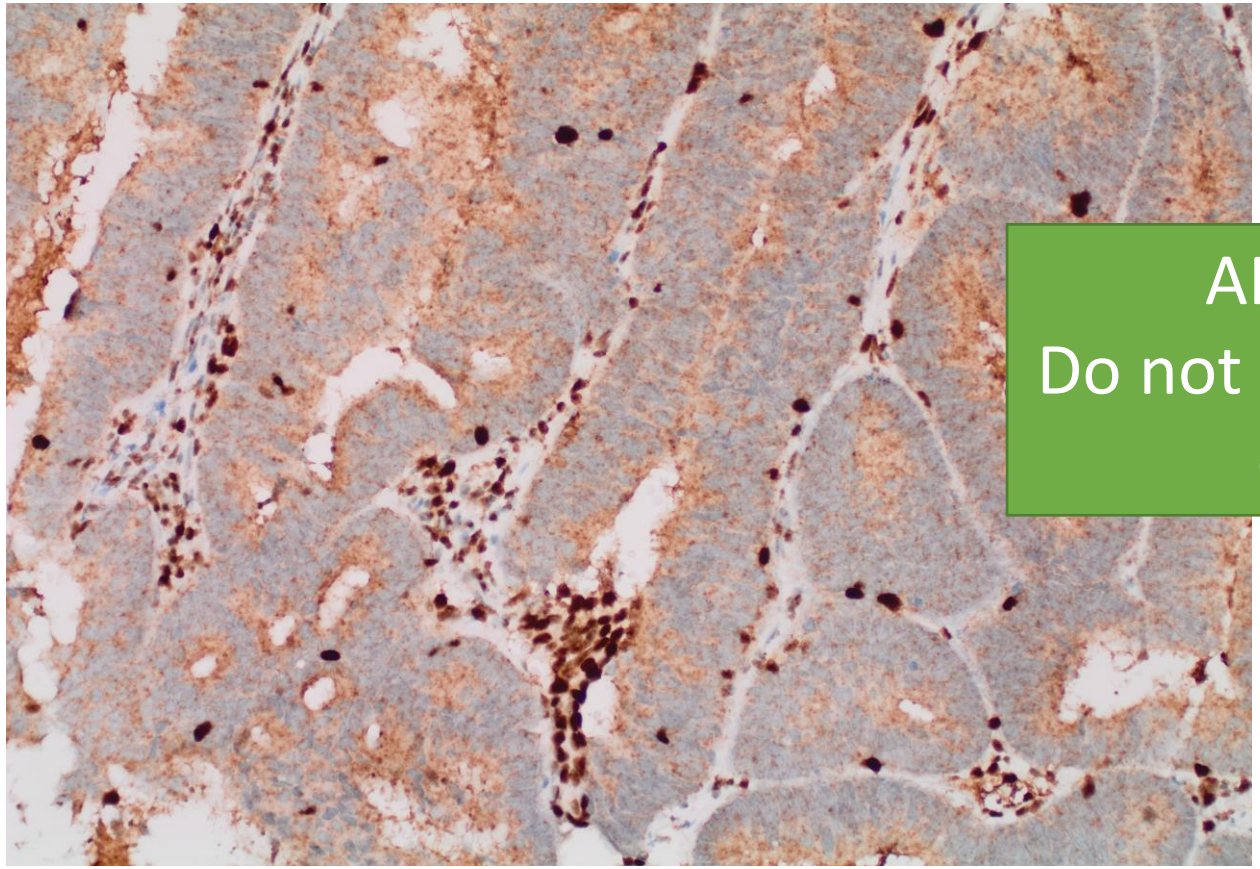
Abnormal Nuclear Membrane Staining Pattern by MLH1 Immunohistochemistry in Endometrioid Adenocarcinoma: A Diagnostic Pitfall

David Jou, Beth Israel Deaconess Medical Center, USA

MMR IHC, Problems and pitfalls: CYTOPLASMIC STAINING



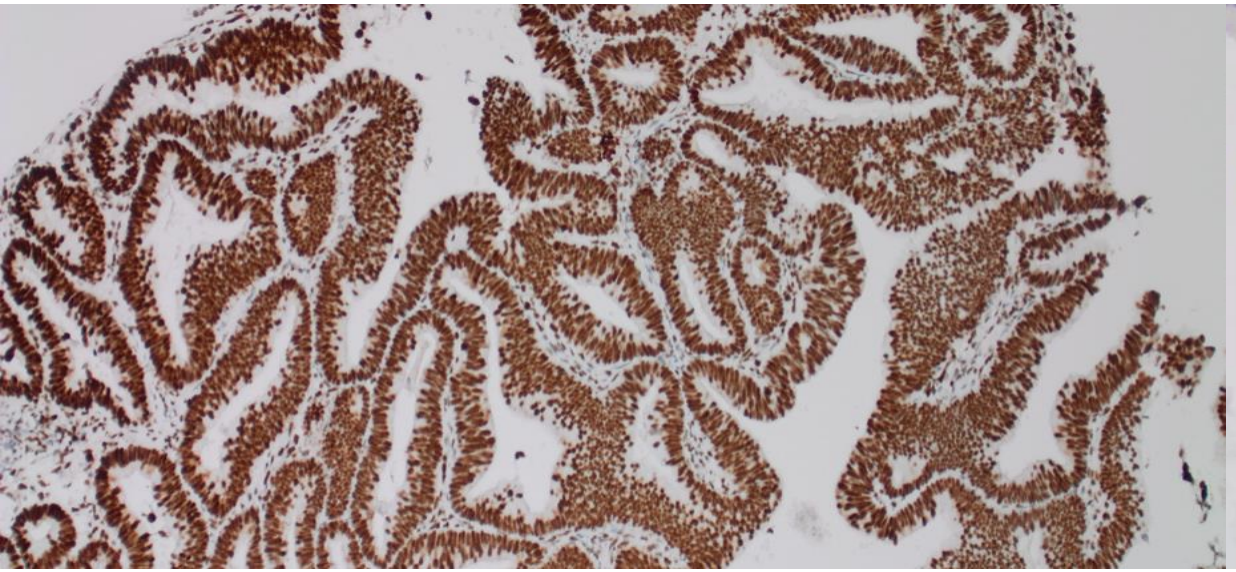
MMR IHC, Problems and pitfalls: CYTOPLASMIC STAINING

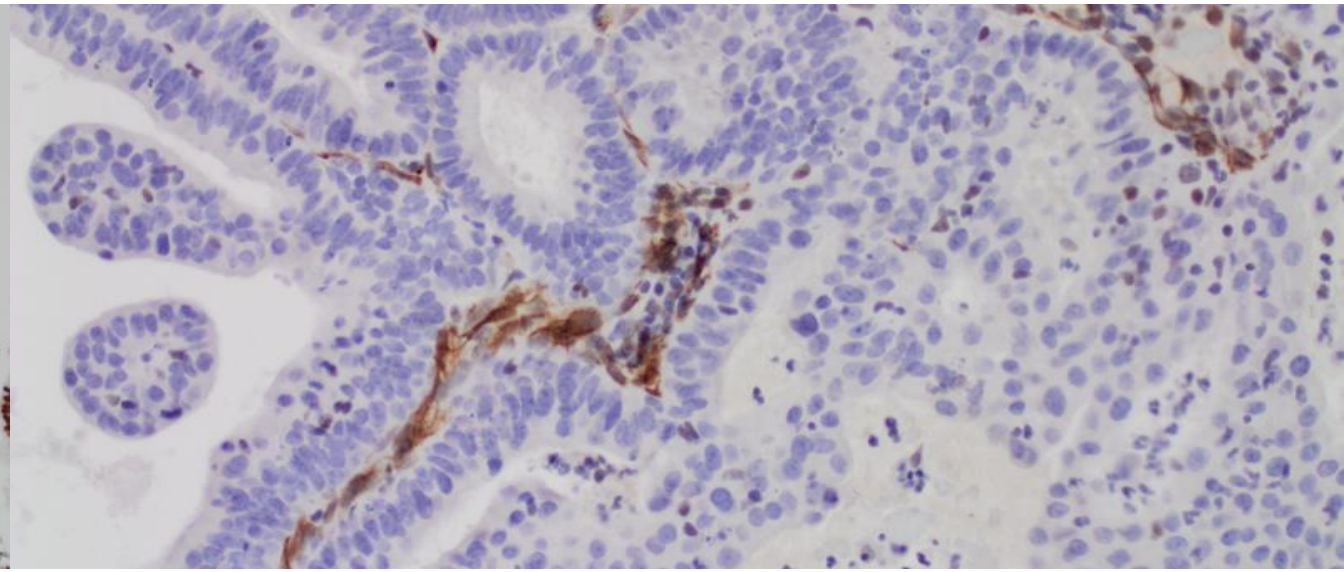


ARTEFACTUAL
Do not interpret as intact expression

MMR IHC: Rare combinations

- Loss of 2 discordant proteins or 3 or all 4
  - MLH1 promoter methylation as sporadic event in MMRd due to any cause
  - MSH6 loss as added mutation in MMRd due to any cause
  - Multiple MMR gene mutations in POLEmut EC; may be subclonal loss
  - Other somatic mutations





How should we report MMR IHC results?

Results: Normal

- All 4 proteins tested, or
- Only PMS2 and MSH6 tested

There is no immunohistochemical evidence of a mismatch repair deficiency*.

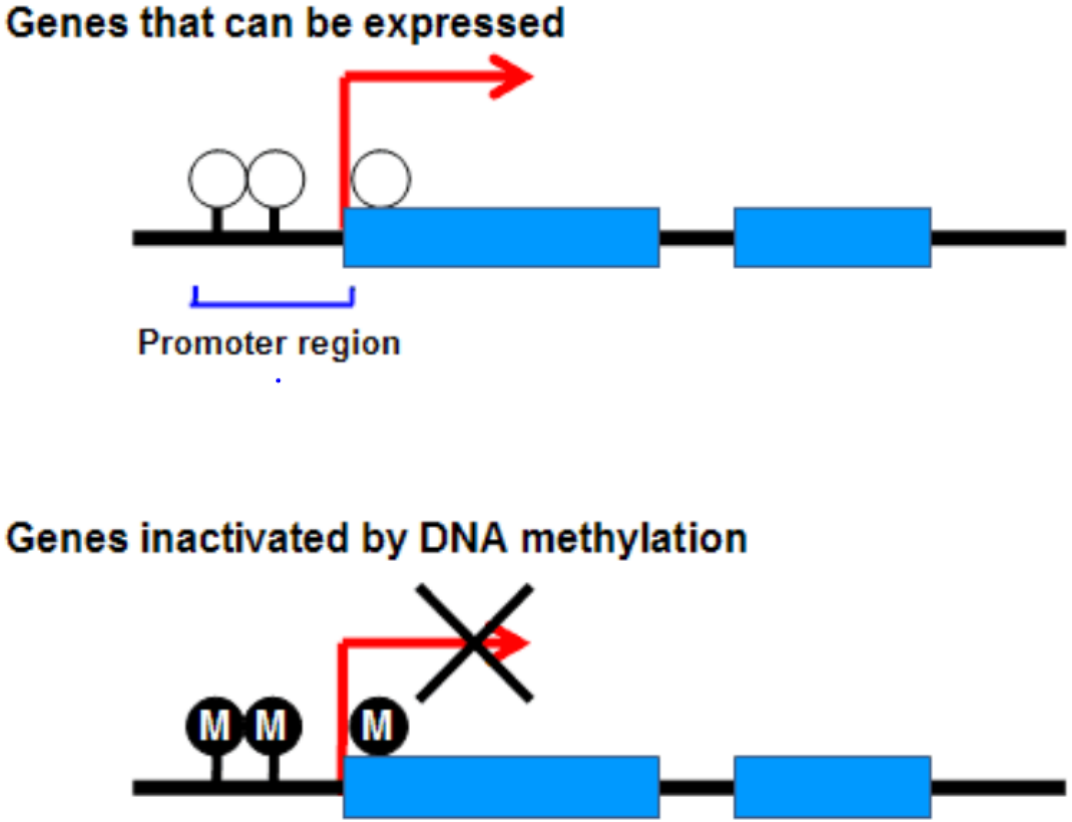
***Referral to Clinical Genetics services should be considered despite this result in the presence of a strong family/clinical history.**

Results: Abnormal (1)

- MLH1 and PMS2 loss

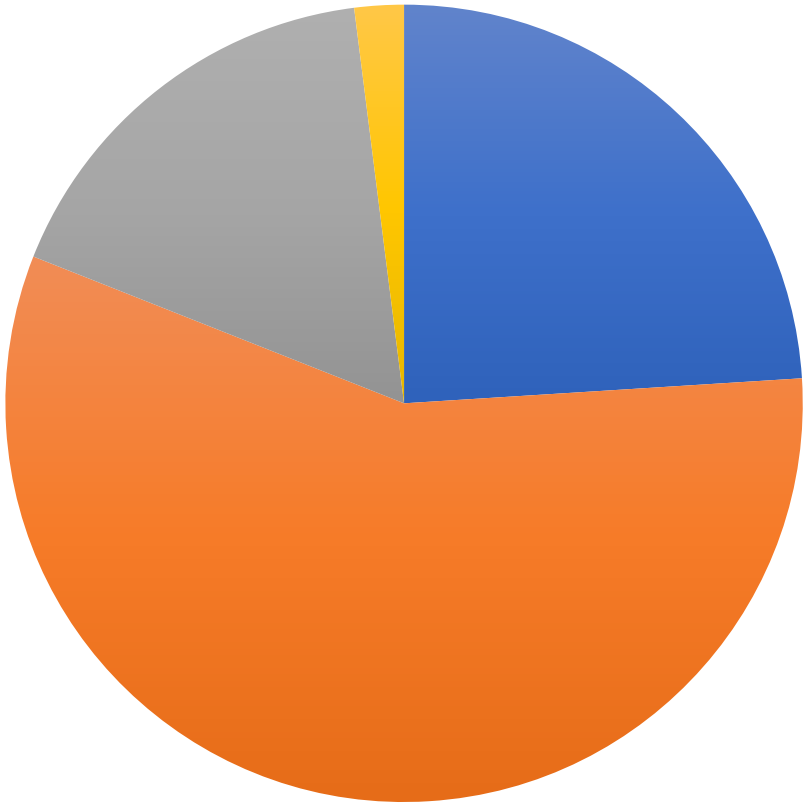
This pattern is likely to be sporadic, although it is possible that this mismatch repair deficiency is due to Lynch or related syndromes. Testing for *MLH1* Promoter hypermethylation is recommended

MLH1 promoter methylation



- >80% of MLH1 loss is due to promoter methylation
- Methylation of the MLH1 promoter silences gene transcription
- Multiple techniques available to detect this in the lab

LS associated EC



Win et al, JNCI 2013

Results: Abnormal (2)

- MSH2 and MSH6 loss
- MSH6 loss
- PMS2 loss
- MLH1 and PMS2 loss **without** *MLH1* promoter methylation

This mismatch repair deficiency is associated with Lynch and related syndromes. This patient should be referred to Clinical Genetics services.

Results: Abnormal (2)

- MSH2 and MSI
- MSH6 loss
- PMS2 loss
- MLH1 and PMS ation

This mismatch r h and related syndromes. This Genetics services.

<50% OF THESE WILL TURN OUT TO BE LS

THE REMAINDER ARE SPORADIC

PRECLUDES NECESSITY FOR CONSENT PRIOR TO THIS STEP

Back to Case 1: *POLE* NGS result

- Mutation status: POSITIVE

- POLE c.857C>G (p.P286R), VAF 34.0%
- POLE c.1227C.A (p.A426E), VAF 8.6%

- Other mutations also present:
- TP53
- ALK
- KIT

POLE Testing in Clinical Practice

- NO IMMUNOHISTOCHEMICAL SURROGATE
- NOT ALL VARIANTS ARE PATHOGENIC
- GUIDELINES ON INTERPRETATION HAVE BEEN FORWARD

POLE Testing in Clinical Practice

- Sequencing of POLE ‘hotspots’: Exons 9, 13 and 14 OR exons 9-14
- Sanger vs NGS depending on throughput/access
- Role of pathologist:
  - Identify suitable tissue: whole section/marked area
  - Indicate tumour nuclear content accurately
  - Provide as sections mounted on slides or rolls or cores

POLE Testing in Clinical Practice: Pathogenic Variants

PROTEIN CHANGE	NUCLEOTIDE SUBSTITUTION
P286R	**c.857C>G**
V411L	**c.1231G>T/C**
S297F	**c.890C>T**
S459F	**c.1376C>T**
A456P	**c.1366G>C**
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

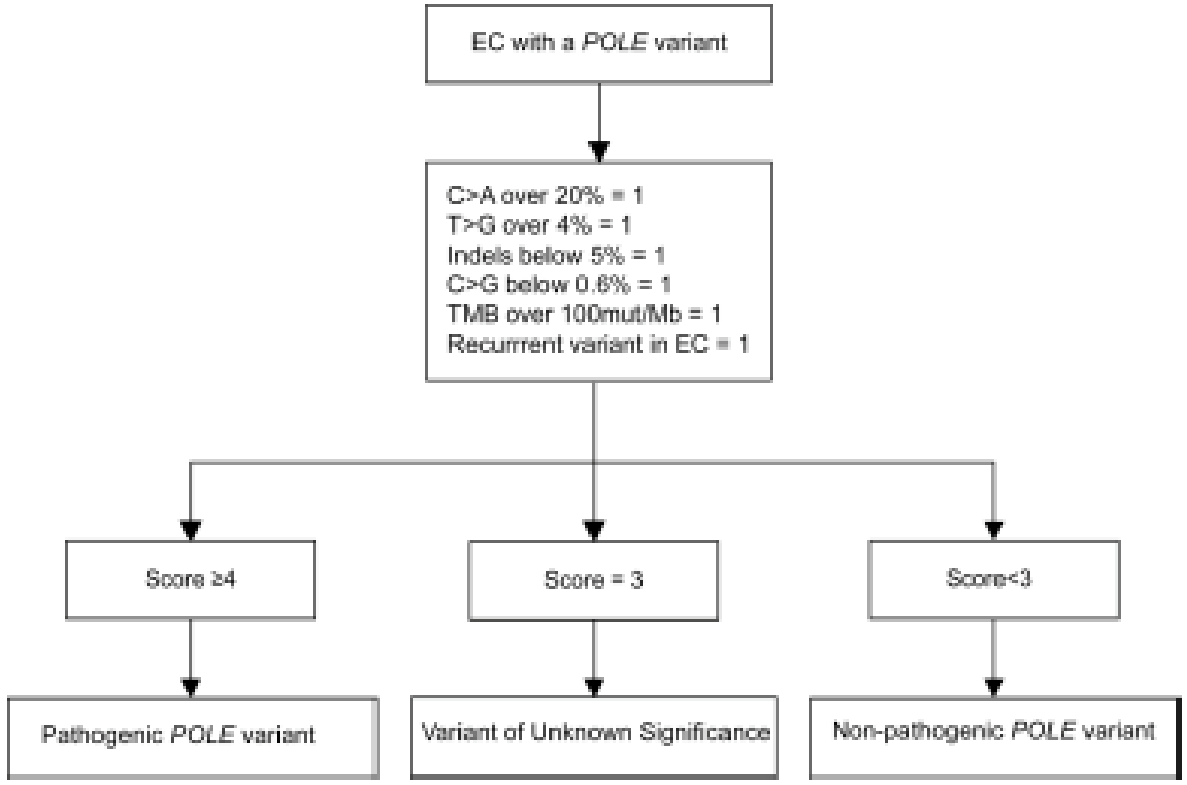
- **EC with of any of these 11 variants should be classified as *POLE*mut**
- **About 2/3rds of all *POLE*mut EC show either P286R or V411L**
- **About 80% *POLE*mut EC show 1 of the top 5 variants (in bold)**

Léon-Castillo et al.
Interpretation of somatic *POLE* mutations in endometrial carcinoma.
J Pathol 2019.
doi:10.1002/path.5372

POLE Testing in Clinical Practice: Non pathogenic variants and VUS

- *POLE* mutations have been reported in 7.7% EC in cohorts other than TCGA
- <10% of these remain to be categorised as pathogenic or not (0.7% of all non-TCGA EC till now)
- Important not to misclassify

POLE Testing in Clinical Practice: Non pathogenic variants and VUS



Léon-Castillo et al.
Interpretation of somatic *POLE* mutations in endometrial carcinoma.
J Pathol 2019.
doi:10.1002/path.5372

Table 6. Recommendations for the interpretation of somatic *POLE* mutations in EC. Recommendations to classify EC with *POLE* mutations with (A) POLE-score available, or (B) POLE-score absent.

A

POLE mutation	Predicted pathogenicity	MSI/MMR status	Treatment recommendation
Exonuclease domain mutation	Pathogenic	MSS/MMRp	*POLE*mut EC
POLE-score ≥4	Pathogenic	MSI/MMRd	*POLE*mut EC[1]
Exonuclease domain mutation	Non-pathogenic	MSS/MMRp	*POLE*wt EC
POLE-score <4	Non-pathogenic	MSI/MMRd	MMRd EC
Non-exonuclease domain mutation	–	MSS/MMRp	NSMP/p53abn EC[2]
	–	MSI/MMRd	MMRd EC

If tumours-only sequencing is performed, detection of L424V variant should prompt consideration of germline testing [37, 38]

B

POLE mutation	Predicted pathogenicity	MSI/MMR status	Treatment recommendation
Exonuclease domain mutation predicted to be pathogenic by ≥4 *in silico* prediction tools	VUS	MSS/MMRp	WES or NSMP/p53abn EC[2,3]
	VUS	MSI/MMRd	WES or MMRd EC[3]
Exonuclease domain mutation predicted to be NON-pathogenic by >1 *in silico* prediction tool	Non-pathogenic	MSS/MMRp	NSMP/p53abn EC[2]
	Non-pathogenic	MSI/MMRd	MMRd EC
Non-exonuclease domain mutation	–	MSS/MMRp	NSMP/p53abn EC[2]
	–	MSI/MMRd	MMRd EC

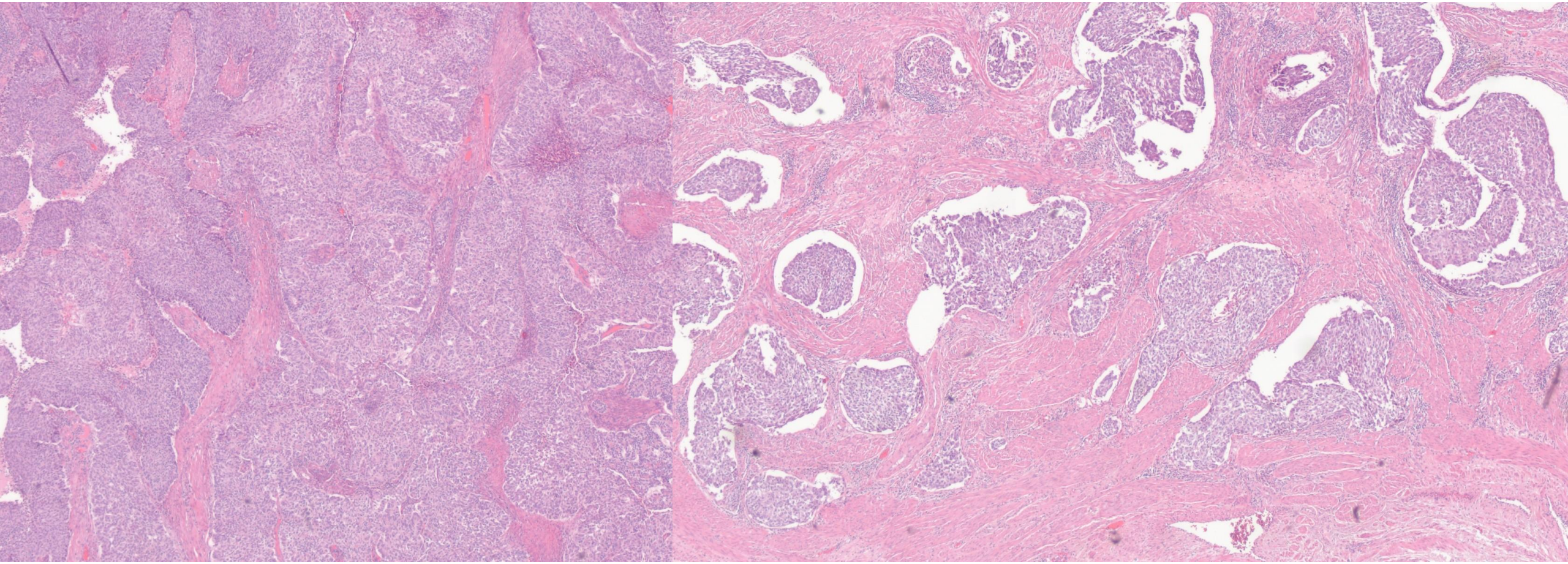
If tumours-only sequencing is performed, detection of L424V variant should prompt consideration of germline testing [39, 40]

1 Treat as *POLE*mut EC (based on genomic alteration) independently of MMR status (insufficient data to suggest otherwise)
2 p53-IHC should be performed to exclude a p53abn EC
3 Treat conservatively i.e. as MMRd/NSMP or send for WES

VUS: Variant of Unknown Significance. NSMP: No Specific Molecular Profile.

Léon-Castillo et al.
Interpretation of somatic *POLE* mutations in endometrial carcinoma.
J Pathol 2019.
doi:10.1002/path.5372

Back to Case 1: Hysterectomy findings



Back to Case 1: Hysterectomy findings

- High grade endometrioid carcinoma
- Involves outer half of myometrium (11/13 mm)
- Extensive LVSI (>5 vessels)
- Omentectomy and sentinel nodes: Negative
- pT1B pN0

Endometrial carcinoma: Epidemiology

- Most common gynaecological cancer in high income countries
- Rising incidence: OBESITY, ageing population; diminishing rates of benign hysterectomy
- Highest rate in North America (86.6/100,000); global increase but max in high-income countries
- Incidence increased across all age groups; cases in women <40 have doubled
- Mortality rates have fallen but absolute number of cancer-related deaths has increased
- Inverse relationship between incidence:mortality ratio and socioeconomic index

Bray F et al. CA Cancer J Clin. 2018;68(6):394-424.
Gu B et al. Gynecol Oncol. 2021;161(2):573-80.
Matsuo K et al. Am J Obstet Gynecol. 2021;224(6):574-84.

Endometrial carcinoma: Epidemiology, summary

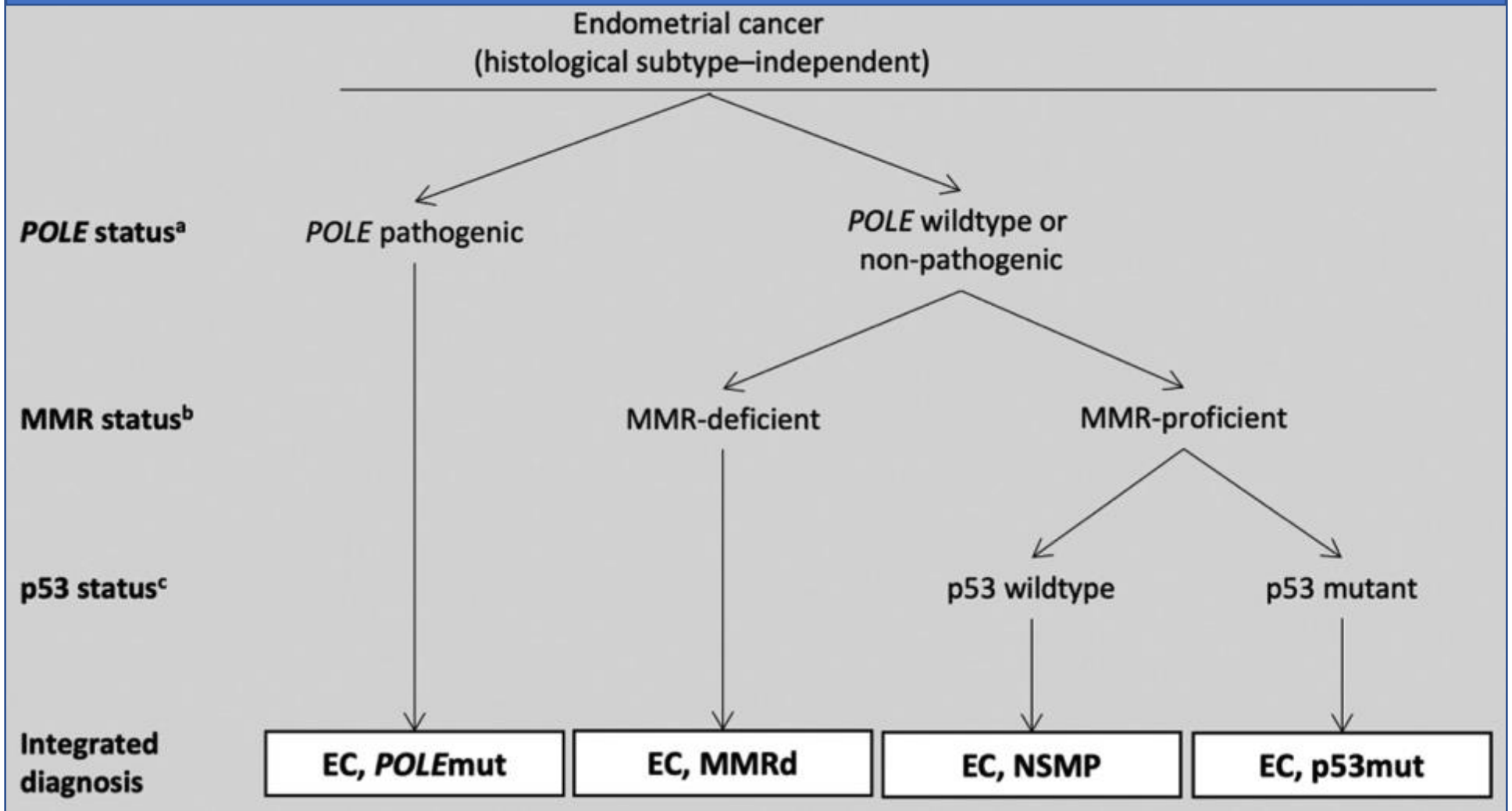
More women are now both dying from and surviving after endometrial cancer than ever before

	Endometrioid	Non-endometrioid
Low Risk	Stage IA, low-grade, negative/focal LVSI	-
Intermediate Risk	Stage IB, low-grade, negative/focal LVSI	Stage IA without myometrial invasion
	Stage IA, high-grade, negative/focal LVSI	
	-	
High-Intermediate Risk	Stage I with substantial LVSI, regardless of grade or depth of invasion	-
	Stage IB, high-grade regardless of LVSI	-
	Stage II	-
High Risk	Stage III-IVA with no residual disease	Stage I-IVA with myometrial invasion and no residual disease

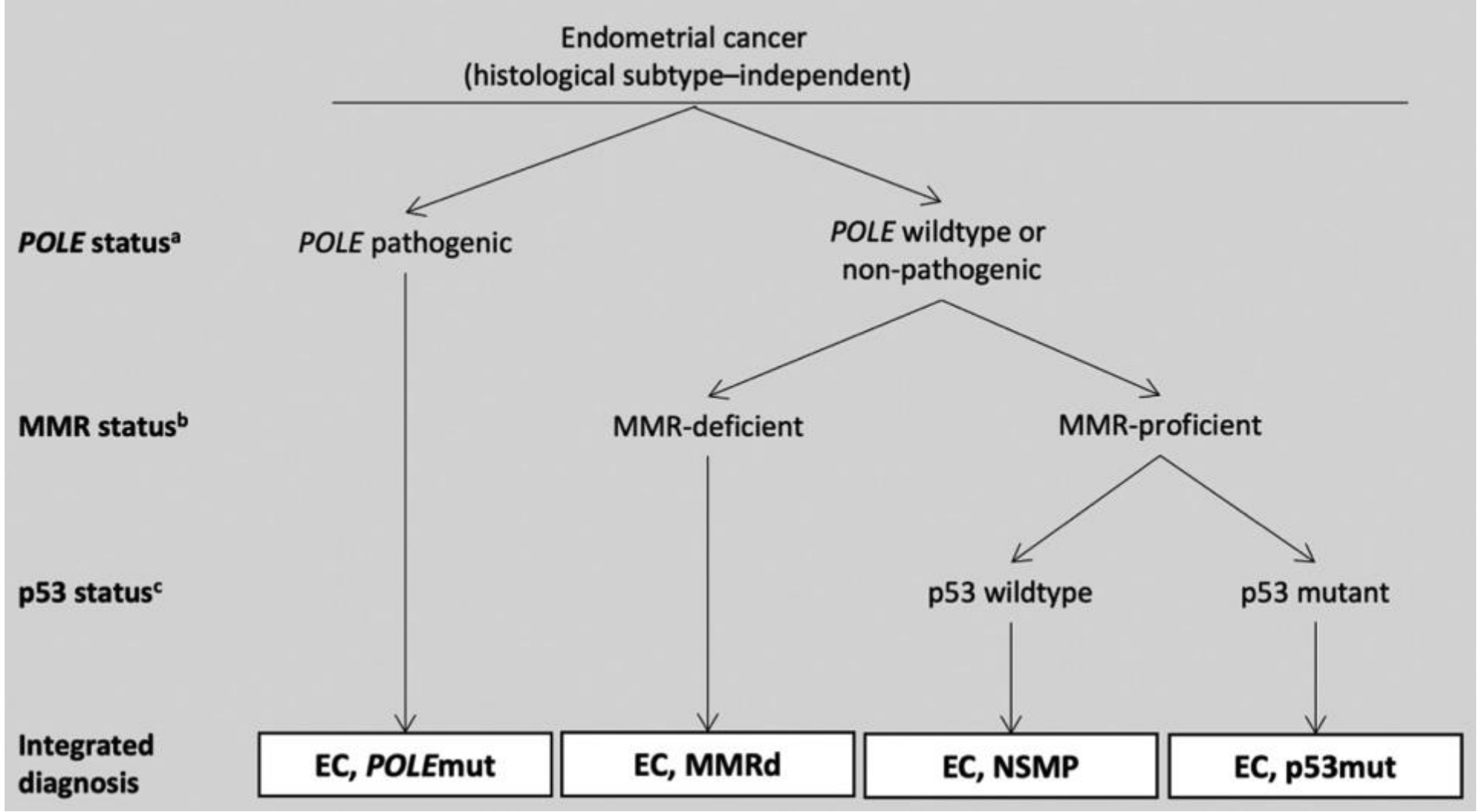
ESGO risk groups, Concin et al, 2020

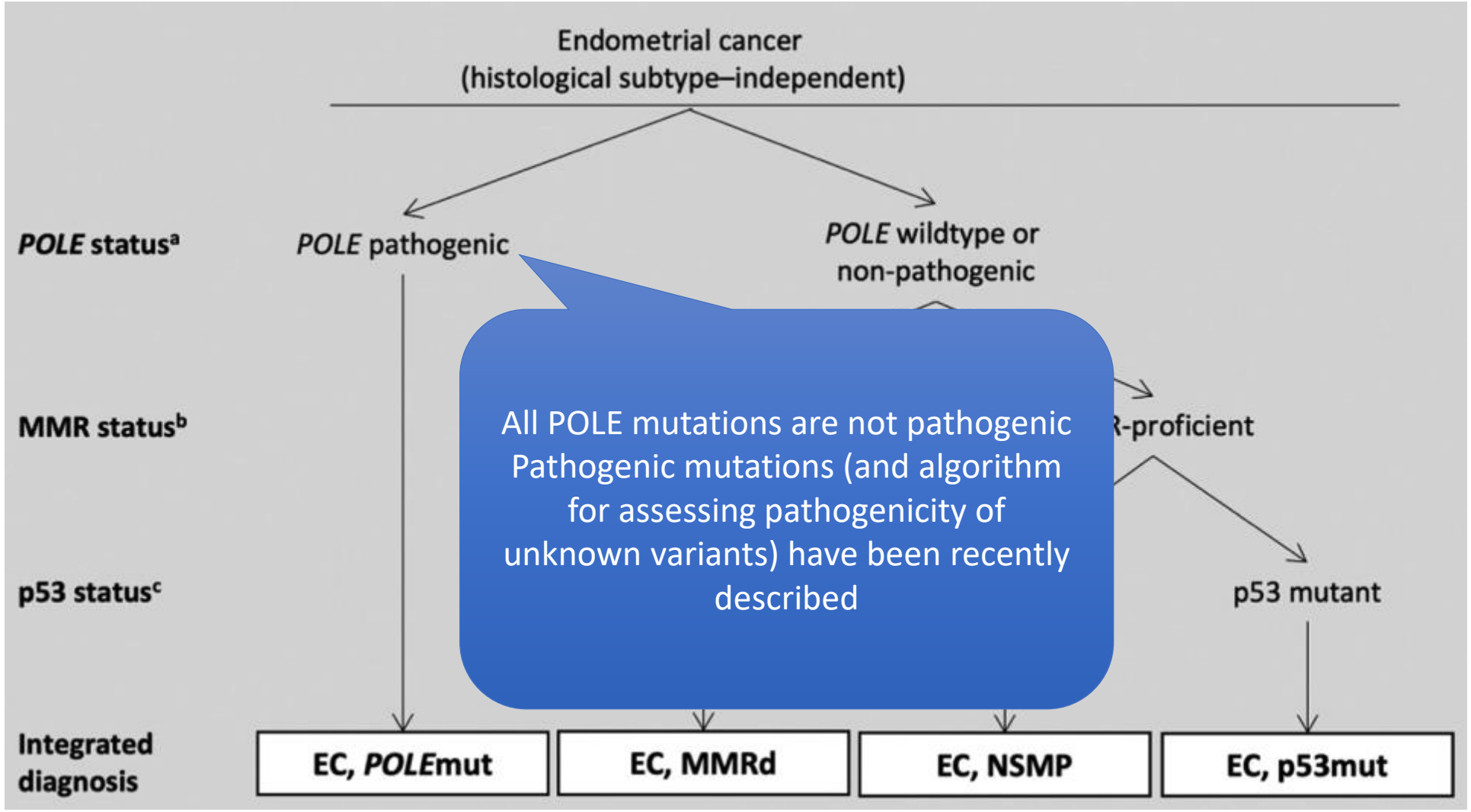
TCGA clusters can be replicated in routine clinical practice using just 3 tests:

- MMR IHC
- p53 IHC
- *POLE* sequencing (Sanger or NGS)

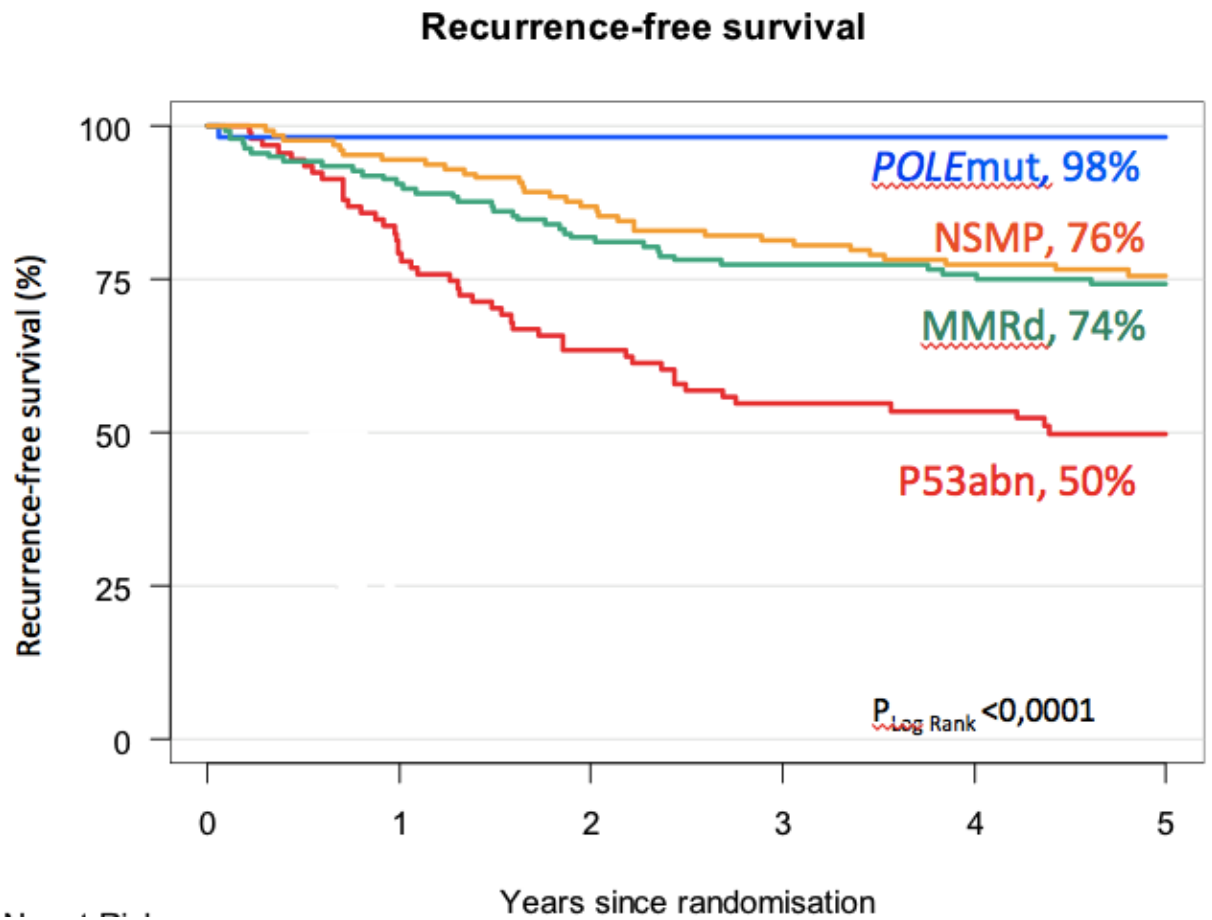


About 3-5% of EC show “multiple classifiers”
This is why we have to interpret these tests in a particular way

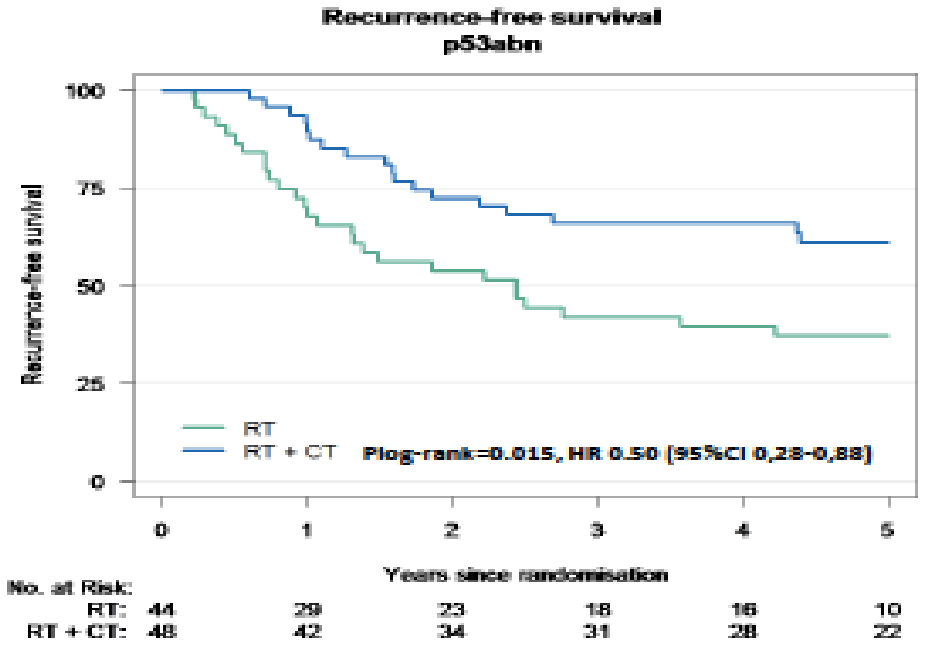


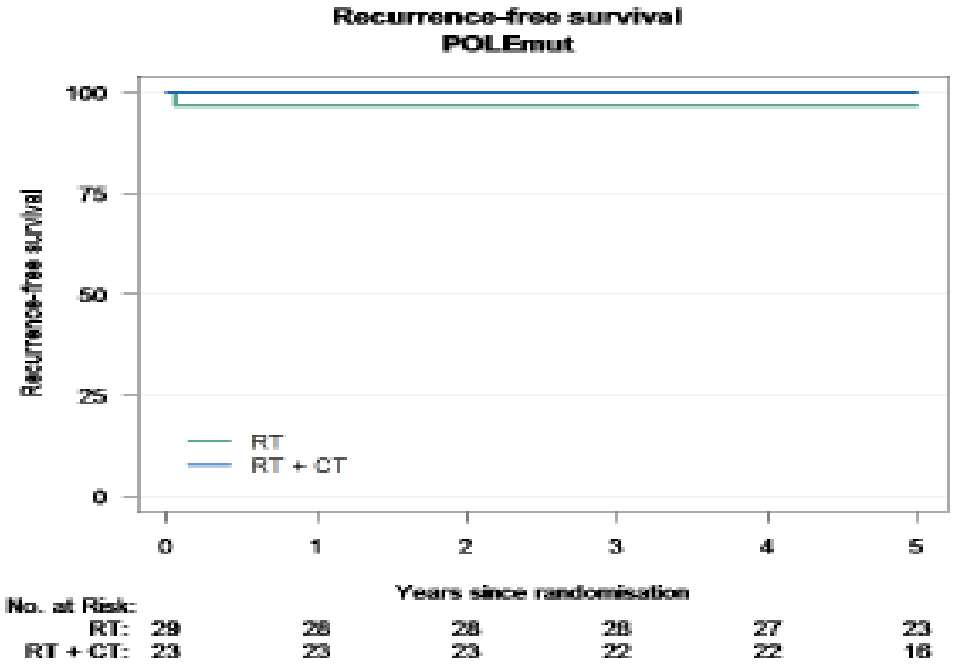

Endometrial cancer
(histological subtype–independent)
POLE status[a]
POLE pathogenic
POLE wildtype or
non-pathogenic
MMR status[b]
-proficient
p53 status[c]
p53 mutant
All POLE mutations are not pathogenic
Pathogenic mutations (and algorithm for assessing pathogenicity of unknown variants) have been recently described
Integrated diagnosis
EC, POLEmut
EC, MMRd
EC, NSMP
EC, p53mut

Molecular groups predict clinical outcomes



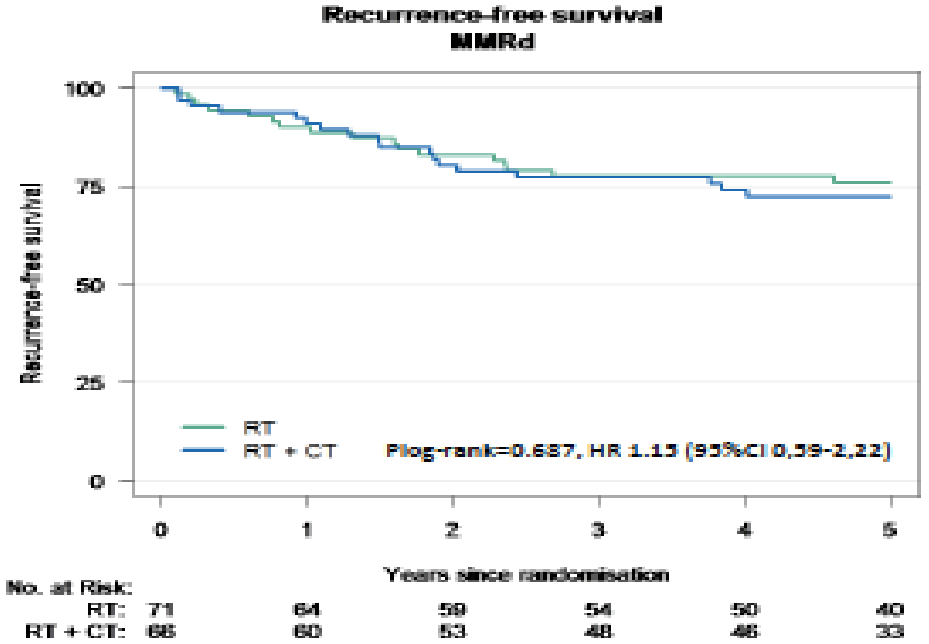
Recurrence-free survival: p53abn and *POLE*mut HREC

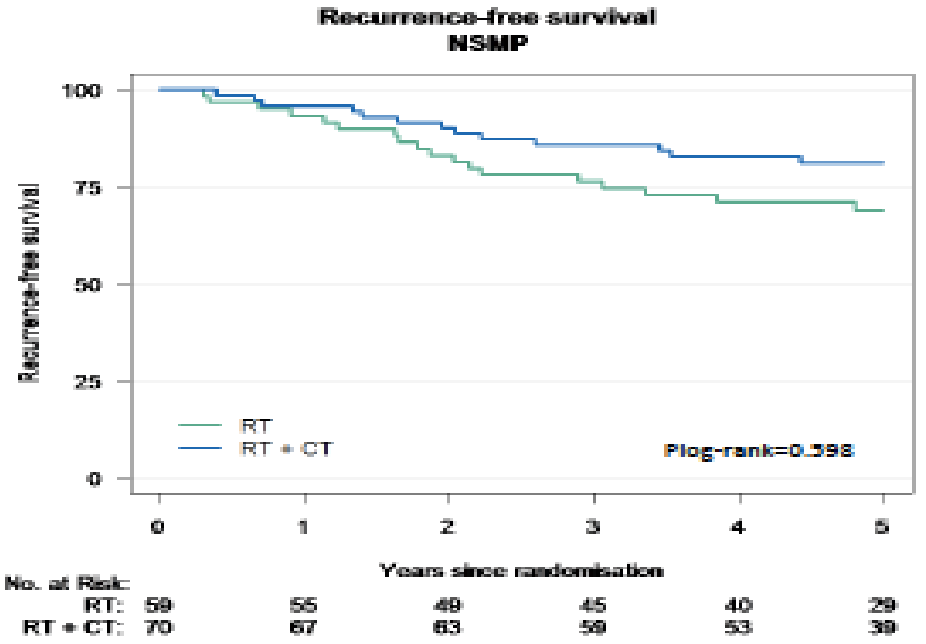




DRAMATIC SURVIVAL IMPROVEMENT WITH CT IN p53ABN

Recurrence-free survival: MMRd and NSMP HREC





NO SURVIVAL BENEFIT WITH CT IN POLEmut or MMRd
TREND TO IMPROVED SURVIVAL IN NSMP

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

2020 risk stratification, molecular classification known:

- MMRd/NSMP:
  - ***Histoype***
  - Grade
  - Stage
  - LVSI
- P53 abn:
  - High-risk except for rare Stage IA without myoinvasion
- POLEmut stage I/II
  - Low-risk

Concin *et al*, IJGC 2020

Risk categorization with and without molecular classification

		With Refined ProMisE Molecular classification					Total
		Low	Intermediate	High-intermediate	High	Advanced metastatic	
Without Molecular Classification	Low	**349 (89.9%)**	**6 (4.6%)**		**3 (1.3%)**		358 (40.0%)
	Intermediate	**10 (2.6%)**	**117 (90.0%)**		**5 (2.2%)**		132 (14.7%)
	High-intermediate	**21 (5.4%)**	0 (0.0%)	**123 (93.9%)**	**21 (9.3%)**		165 (18.4%)
	High	**8 (2.1%)**	**7 (5.4%)**	**8 (6.1%)**	**198 (87.2%)**		221 (24.7%)
	Advanced metastatic					**20 (100.0%)**	20 (2.2%)
	Total	388 (43.3%)	130 (14.5%)	131 (14.6%)	227 (25.3%)	20 (2.2%)	896 (100%)

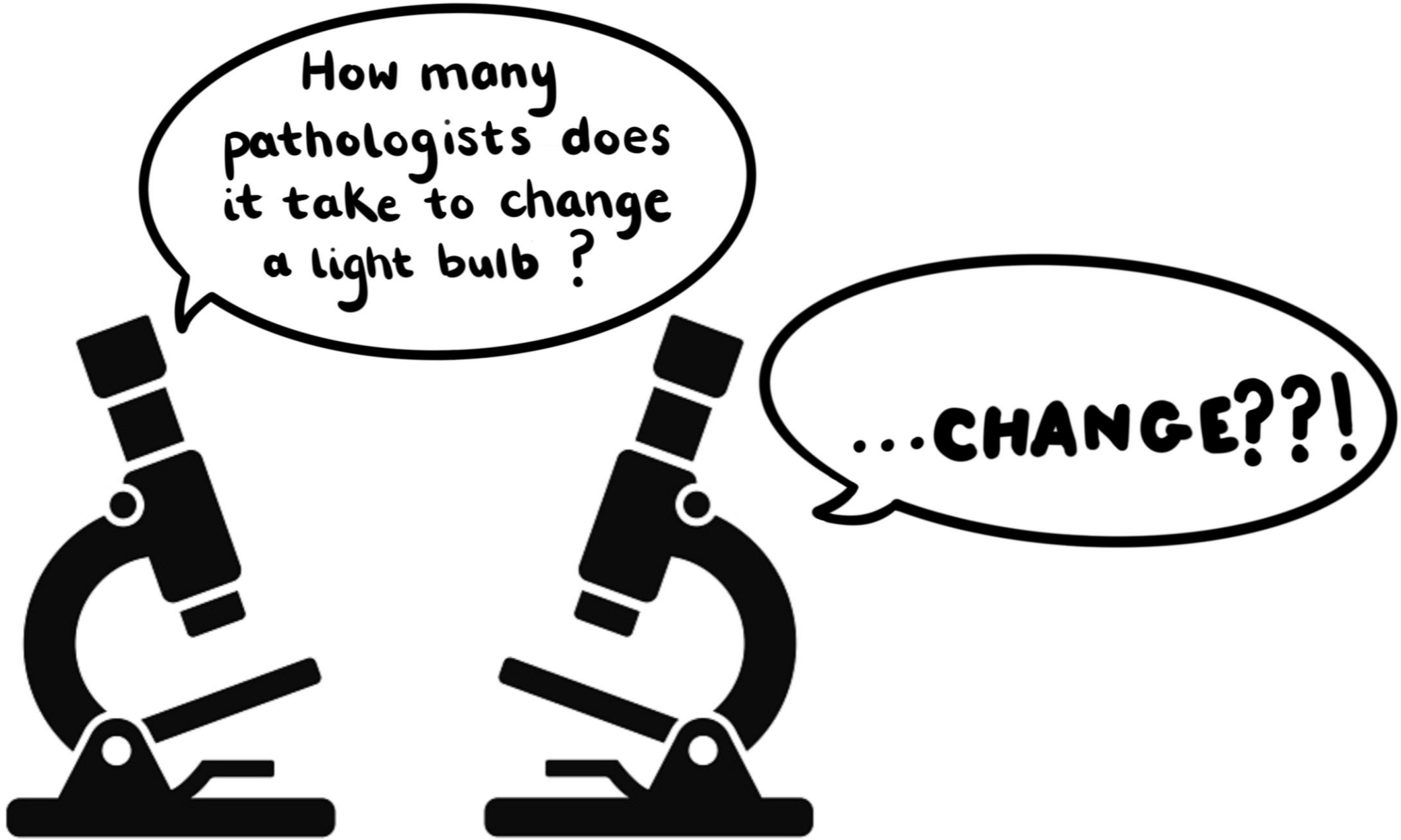
Molecular classification changed the risk category in 89/899 (10%) cases:

- **6% → lower group**
- **4% → higher group**

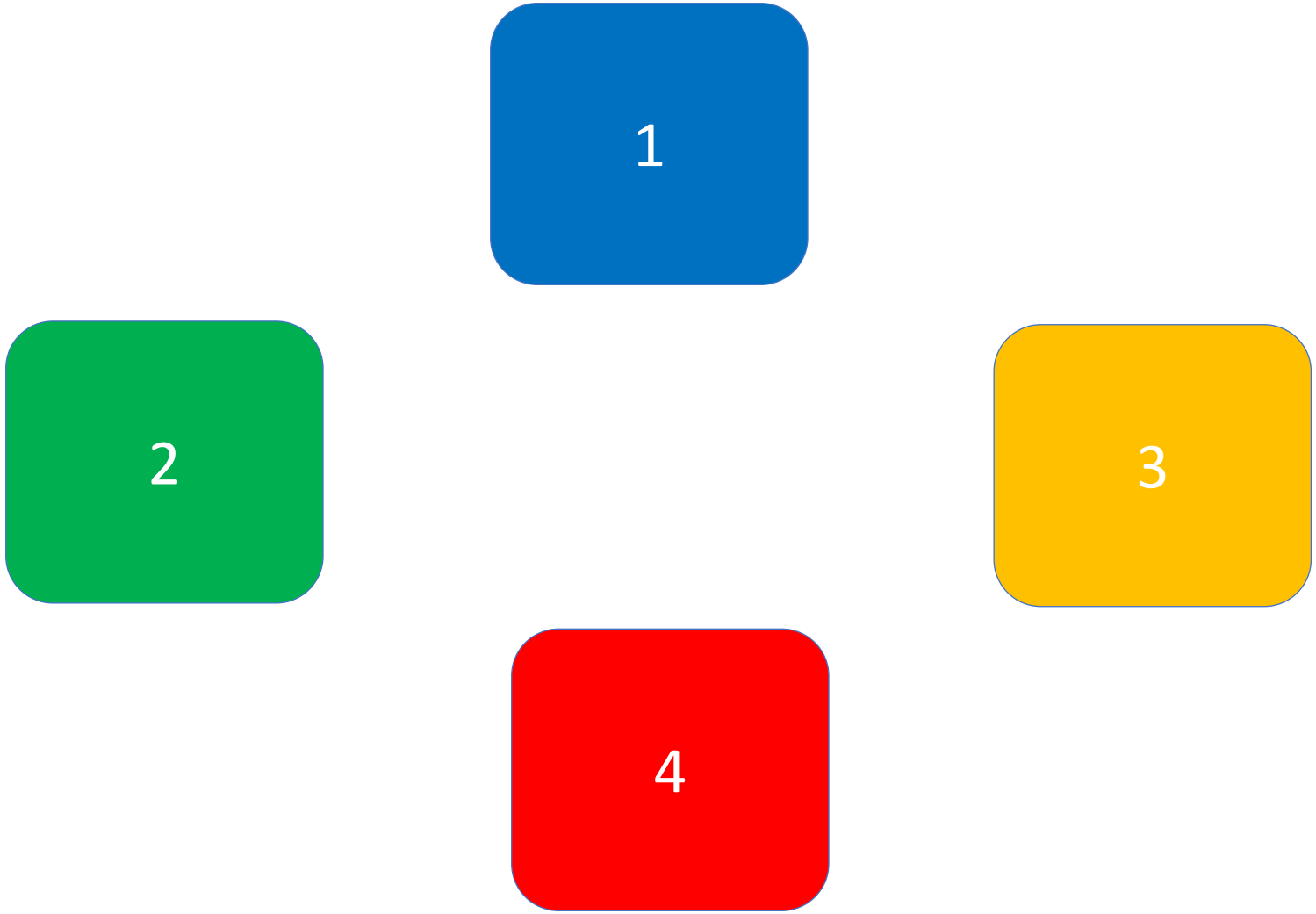
Talhouk et al, IJGP 2022, manuscript under review

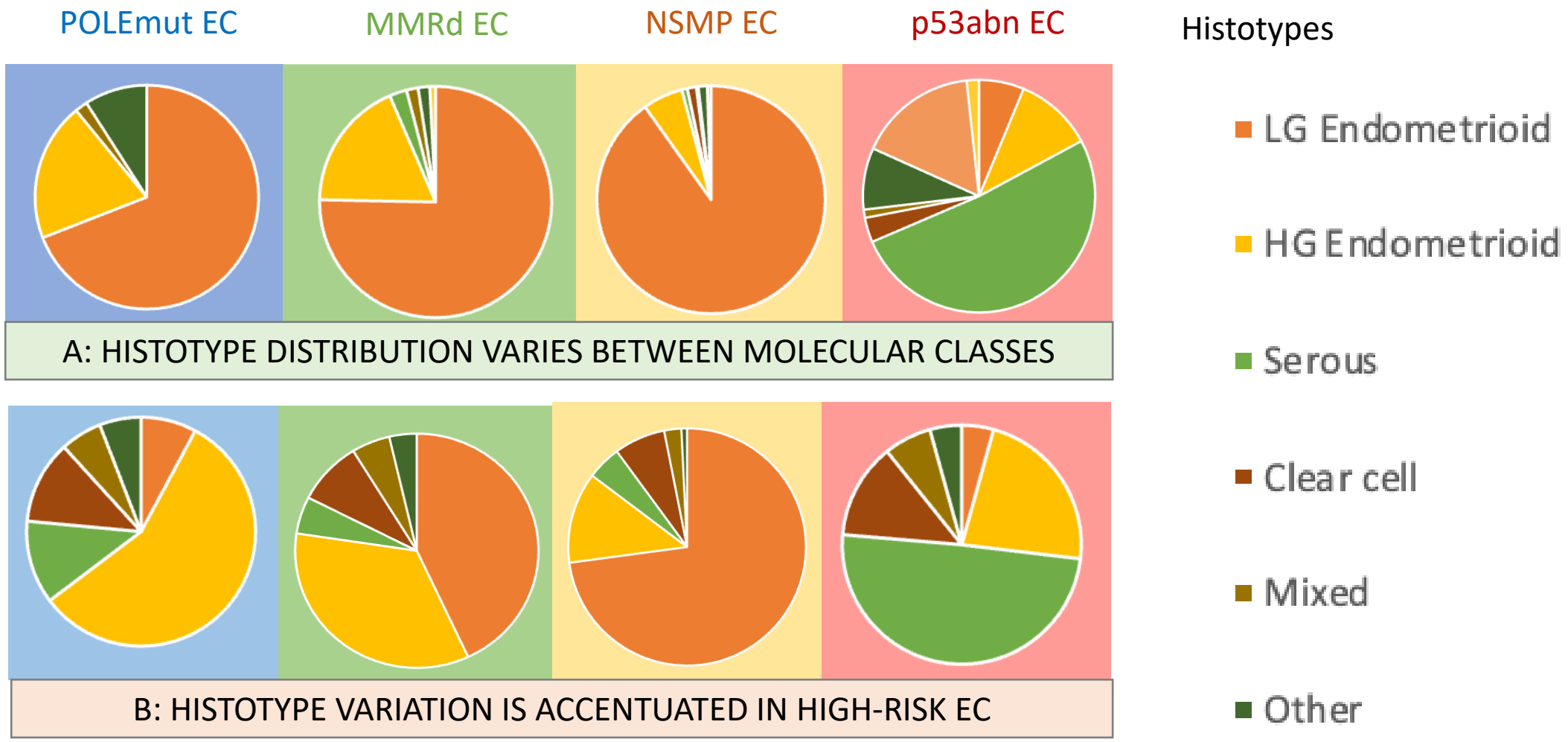
Molecular classification:

- Improves risk prediction
- Predicts treatment response
- Can be replicated with simple tests
- MAJOR IMPACT IS ON PERSONALISED TREATMENT AND THEREBY IMPROVING PATIENT OUTCOMES

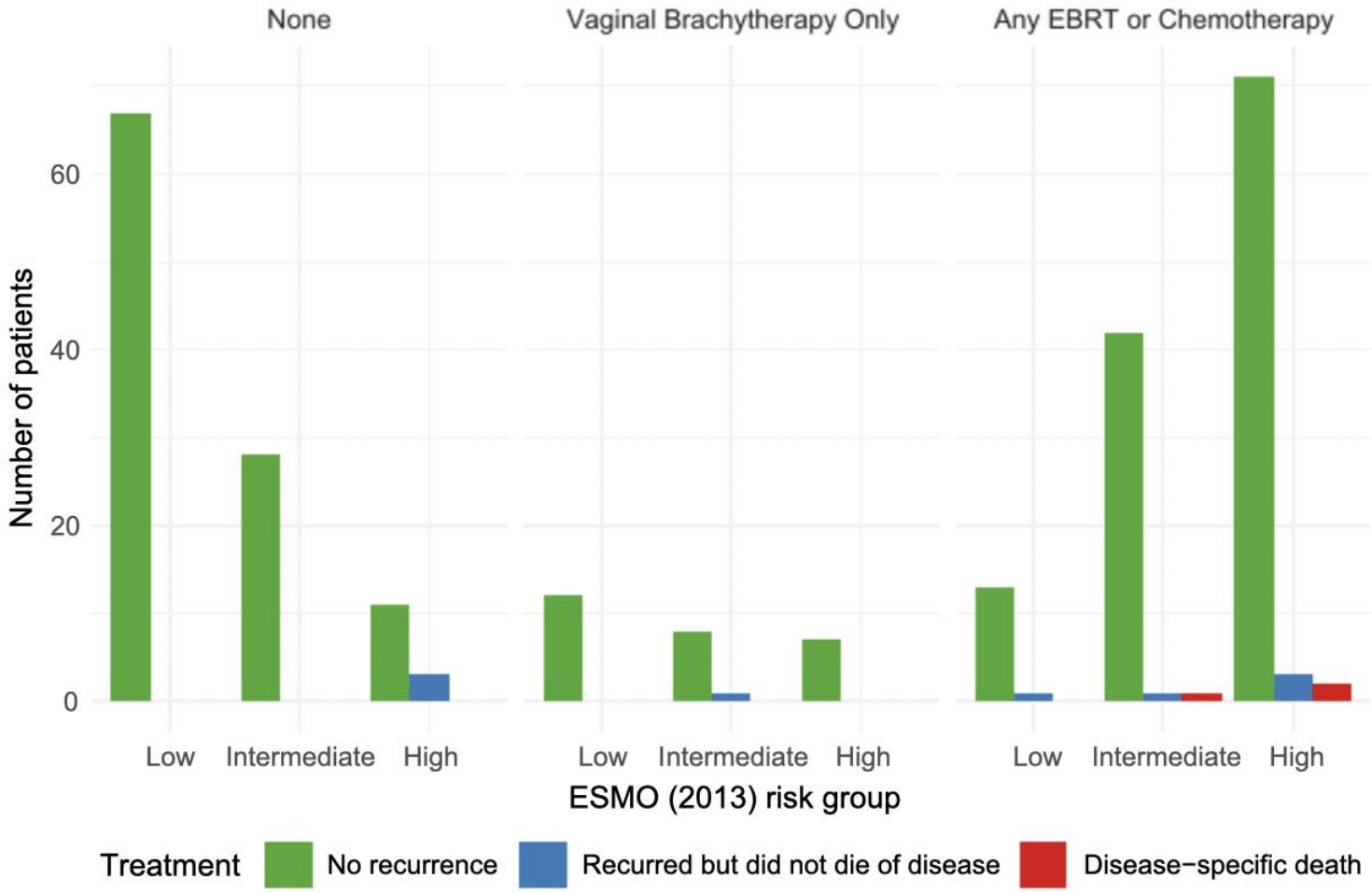

How many pathologists does it take to change a light bulb ?
...CHANGE?!

TCGA (2013): EC fall into 4 groups not 2




POLEmut EC
MMRd EC
NSMP EC
p53abn EC
A: HISTOTYPE DISTRIBUTION VARIES BETWEEN MOLECULAR CLASSES
B: HISTOTYPE VARIATION IS ACCENTUATED IN HIGH-RISK EC
Histotypes
LG Endometrioid
HG Endometrioid
Serous
Clear cell
Mixed
Other

Clinical Outcomes of POLEmut cases are outstandingly good, regardless of risk category and adjuvant Rx



- IPD meta-analysis from 13/15 eligible studies reporting POLE mutated EC with outcomes
- 294/359 had ***pathogenic*** POLE mutations (HR 3.42)
- 12 events (recurrence/progression)
- 3 disease-specific deaths
- Only stage was prognostic
- 42 cases int/high risk with no adjuvant Rx; 3 recurrences, no death
- 8/134 events in cases Rxed with EBRT +/- chemo

McAlpine et al, Cancer 2021; https://doi.org/10.1002/cncr.33516

MMRd EC: Management implications

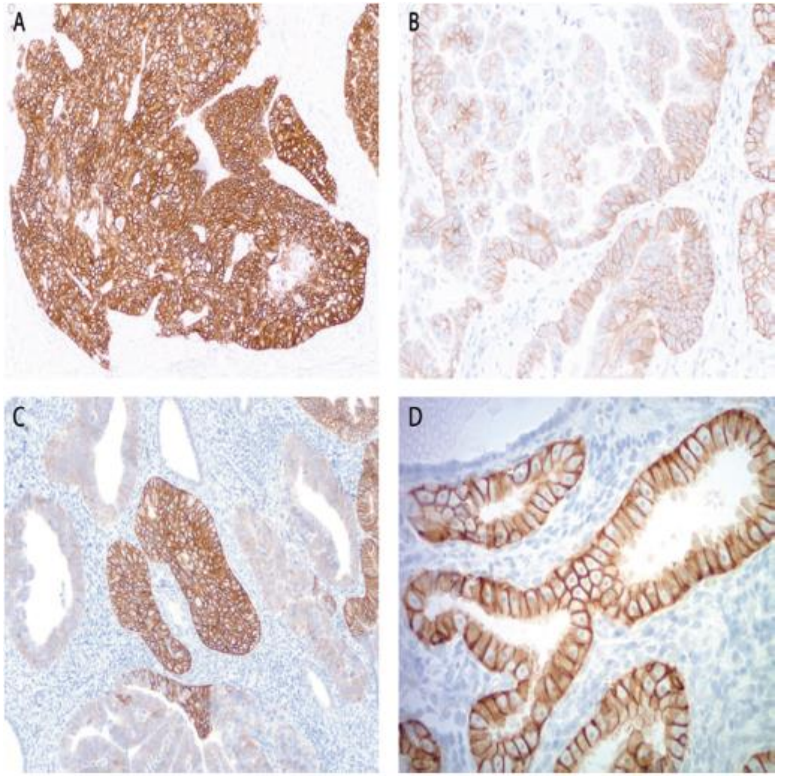
- **Lynch Syndrome screening**
- **Molecular classification; prognosis**
- **Disease classification (endometrioid, not ‘serous’)**
- **High radiation-sensitivity**
- **Low chemosensitivity**
- **?Response to hormonal Rx**
- **Immune checkpoint inhibitor Rx**

NSMP EC: Management Implications

- **Intermediate to excellent prognosis**
- **Heterogeneous group**
- **Further molecular classes will emerge**
- **Histotype and grade remain prognostically important**
- **Chemoresponsiveness inconclusive**
- **Most likely to respond to hormonal Rx (Progesterone, metformin)**

P53 abn EC: Rx implications

- Chemosensitivity
- HRD EC and PARP inhibitor therapy
- HER2 positivity in TCGA (25/25) and PORTEC3 (23/24) cohorts is exclusively in p53abn group
- Immune checkpoint (combination therapies)



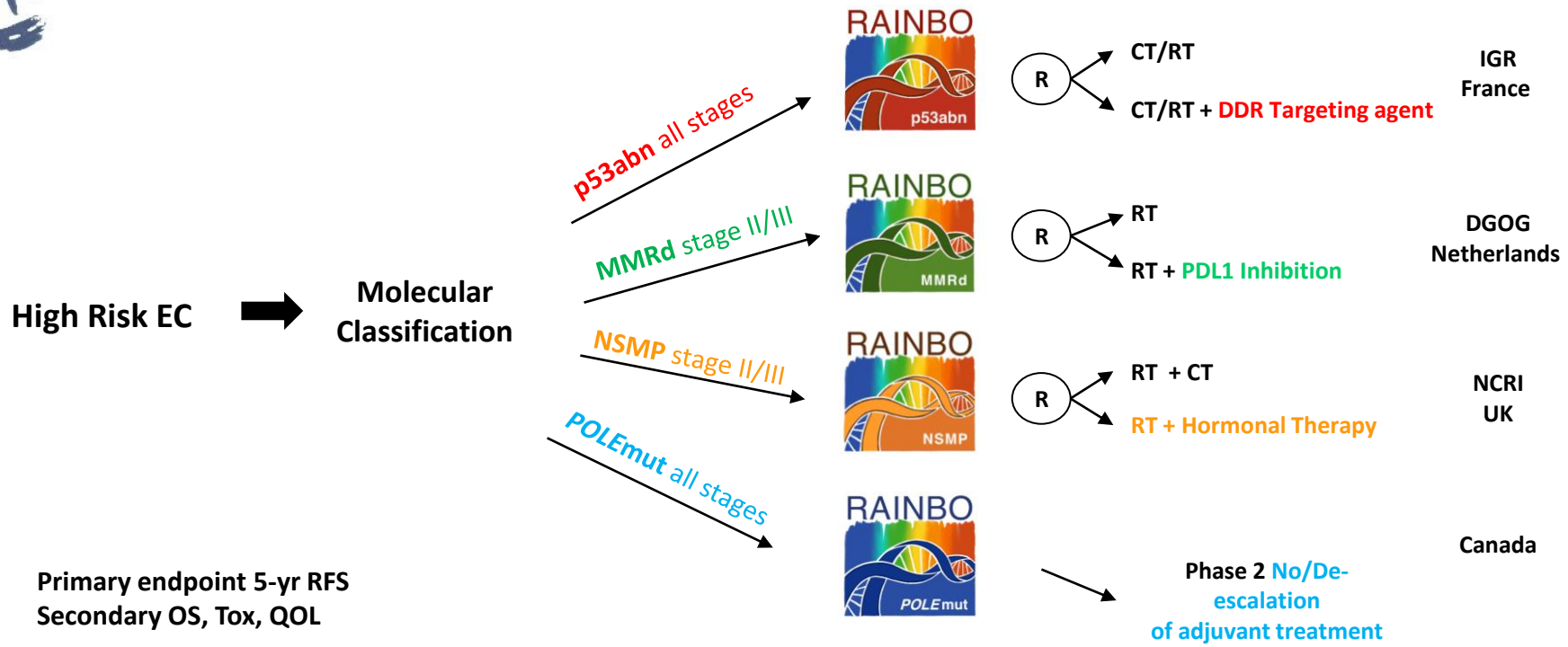
Vermij et al, Cancers 2021)

2. We need prospective clinical trial data



RAINBO Trial

Refining Adjuvant Treatment In Endometrial Cancer Based On Molecular Features



Primary endpoint 5-yr RFS
Secondary OS, Tox, QOL

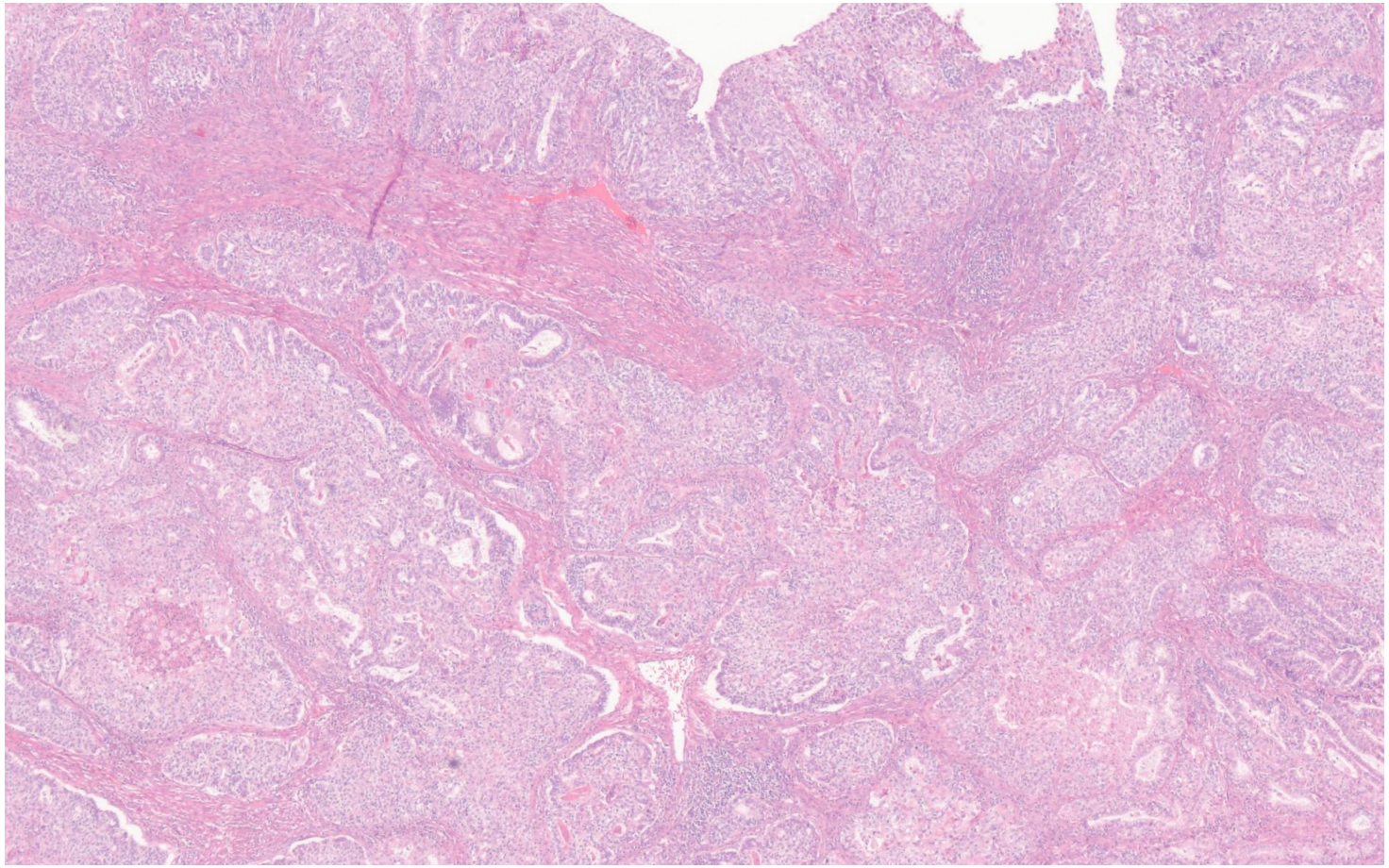
Back to Case 1: Adjuvant treatment and follow-up so far

- Classically regarded as high-risk: G3 endometrioid, pT1B pN0; extensive LVSI
- Current trend to de-escalation and clinical equipoise discussed
- Patient apprehensive about observation alone
- Proceeded to adjuvant chemotherapy with pelvic radiotherapy
- Last clinic visit (after first cycle): Tearful and quite sad (hair); Hair loss and reported nausea, vomiting, fatigue, paraesthesias in both hands
- Fearful about next cycle.

Case 2

- 51F
- Biopsy proven FIGO grade 2/3 endometrioid carcinoma
- MMR and p53 normal

Case 2: Hysterectomy



Case 2: Hysterectomy

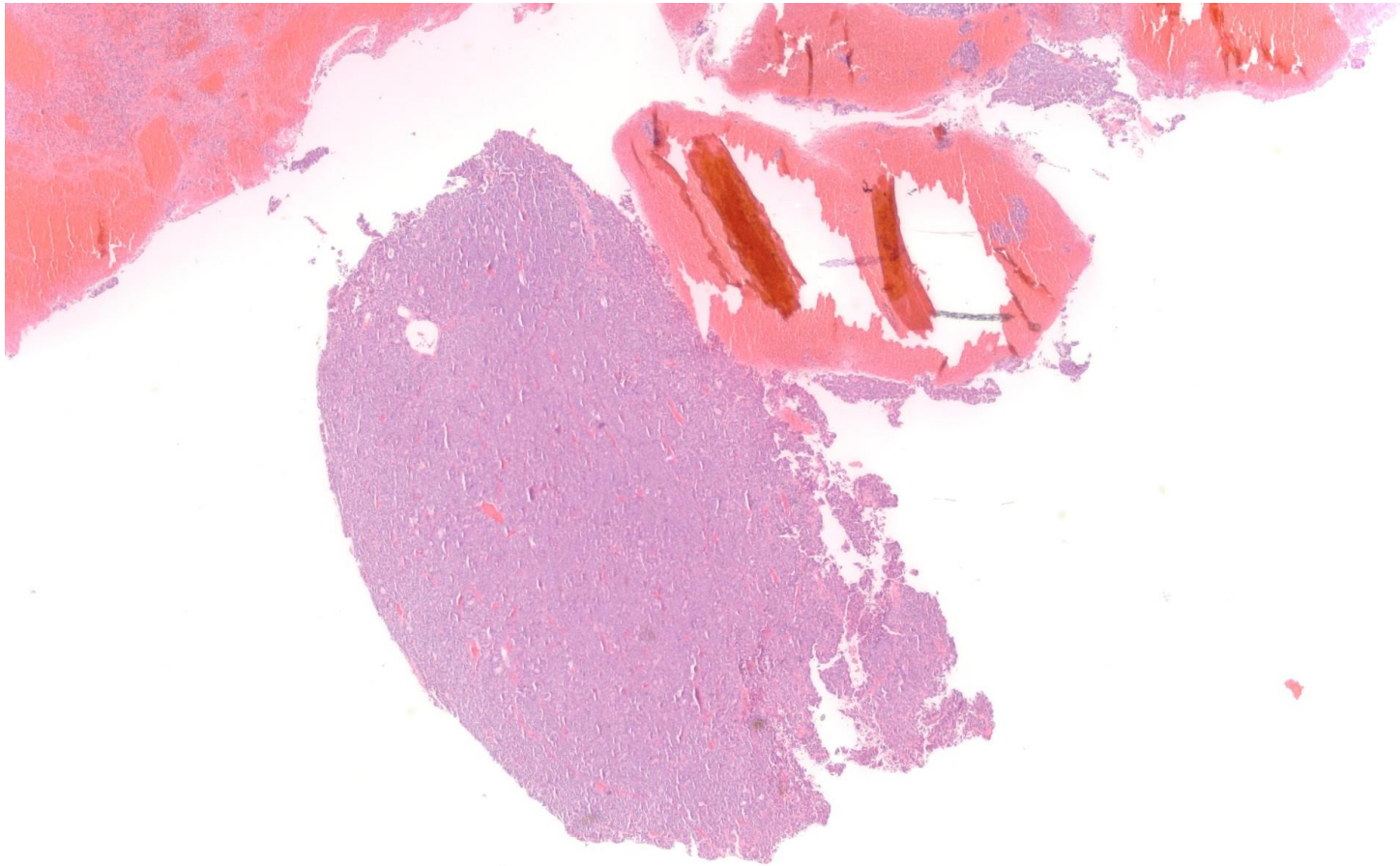
- Grade 3 endometrioid carcinoma
- Invading outer myometrium
- Negative for LVSI
- Sentinel nodes negative
- pT1B pN0

- Enrolled in TAPER trial
- Strongly considering observation due to chronic side effects of pelvic RT (bowel habit, vaginal stenosis/agglutination and sexual dysfunction)

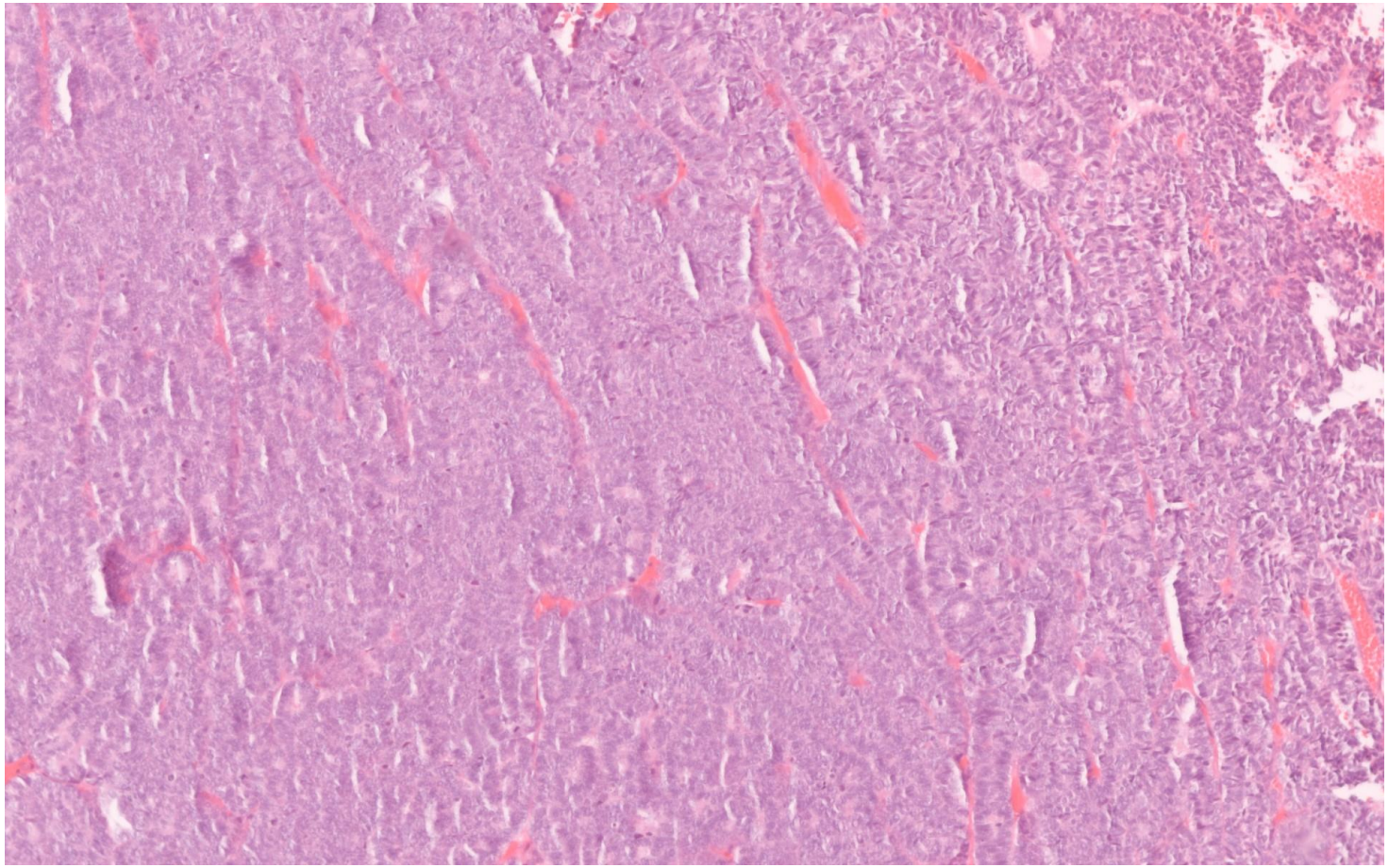
Case 3

- 81F
- Heavy PMB x 1 month
- Large friable polyp protruding through cervical canal ?endometrial or endocervical in origin
- D&C

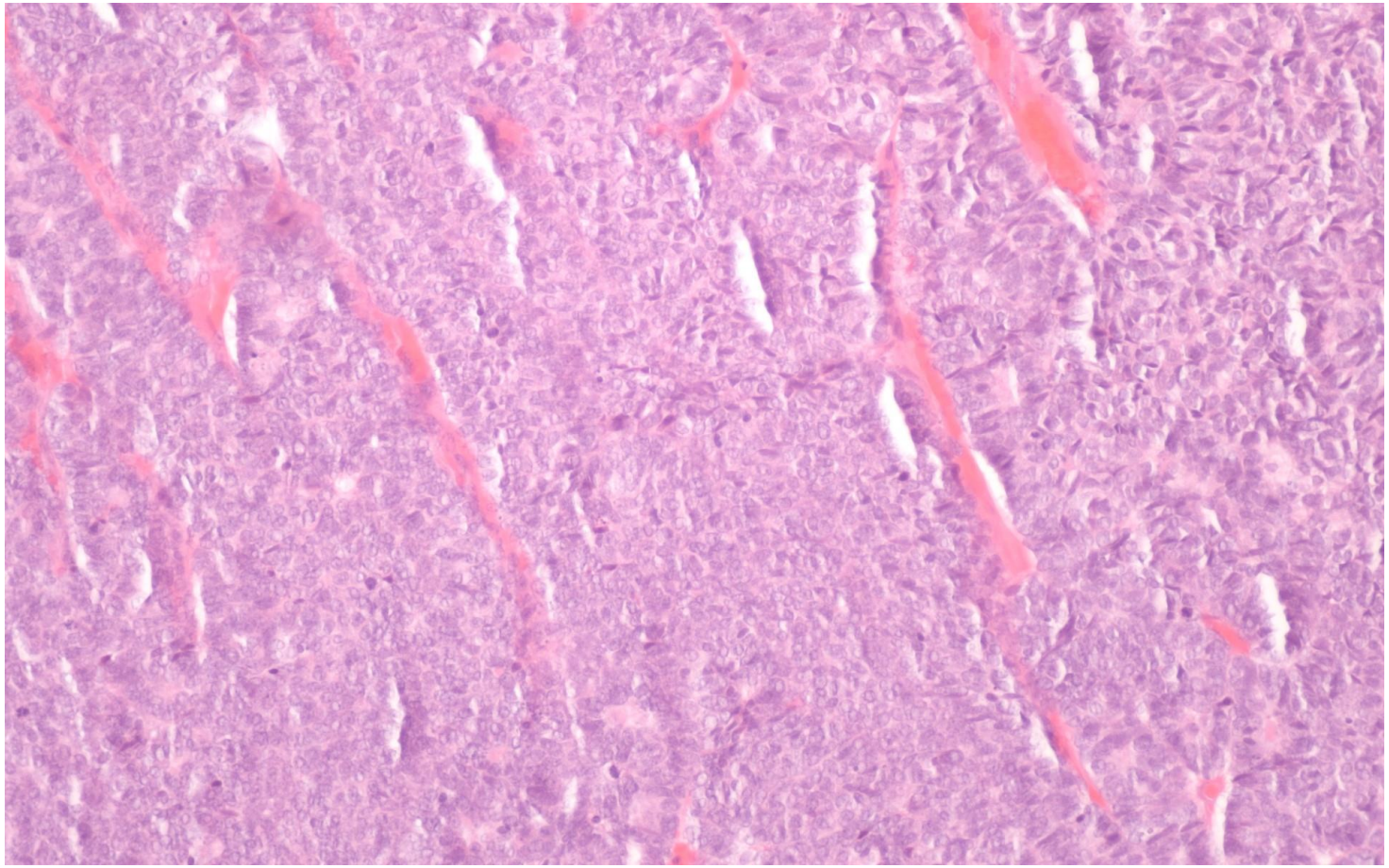
Case 3: Biopsy



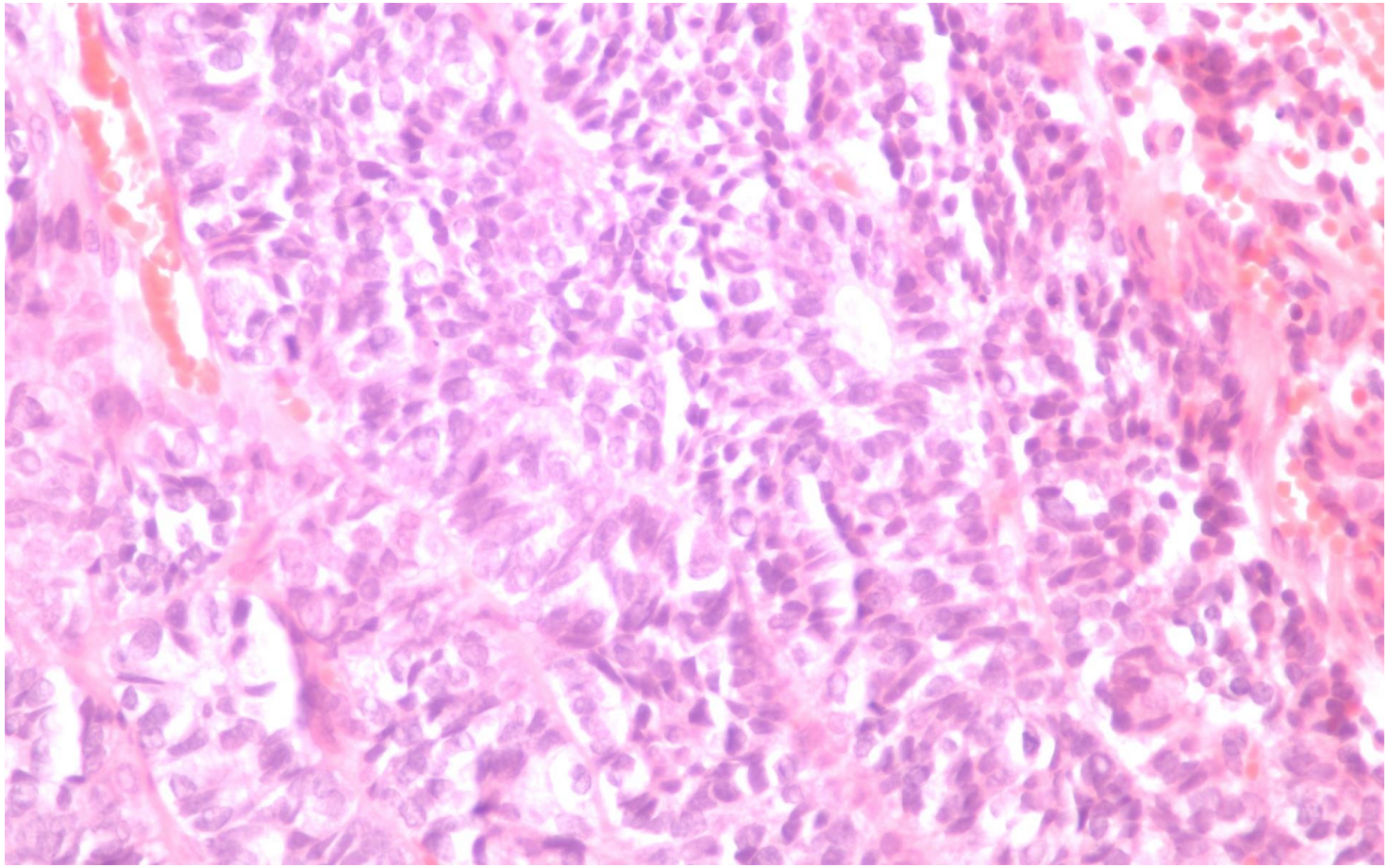
Case 3: Biopsy



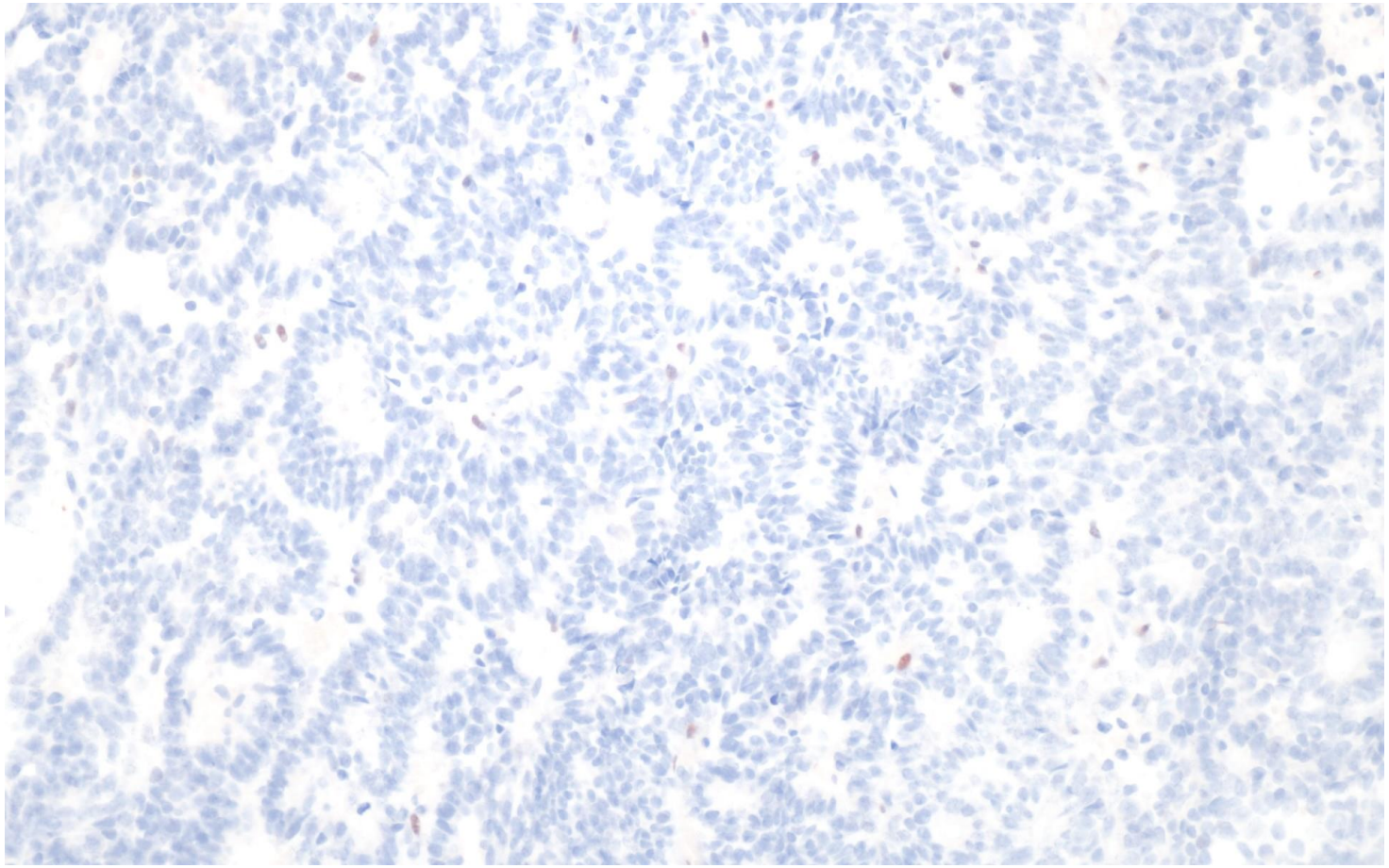
Case 3: Biopsy



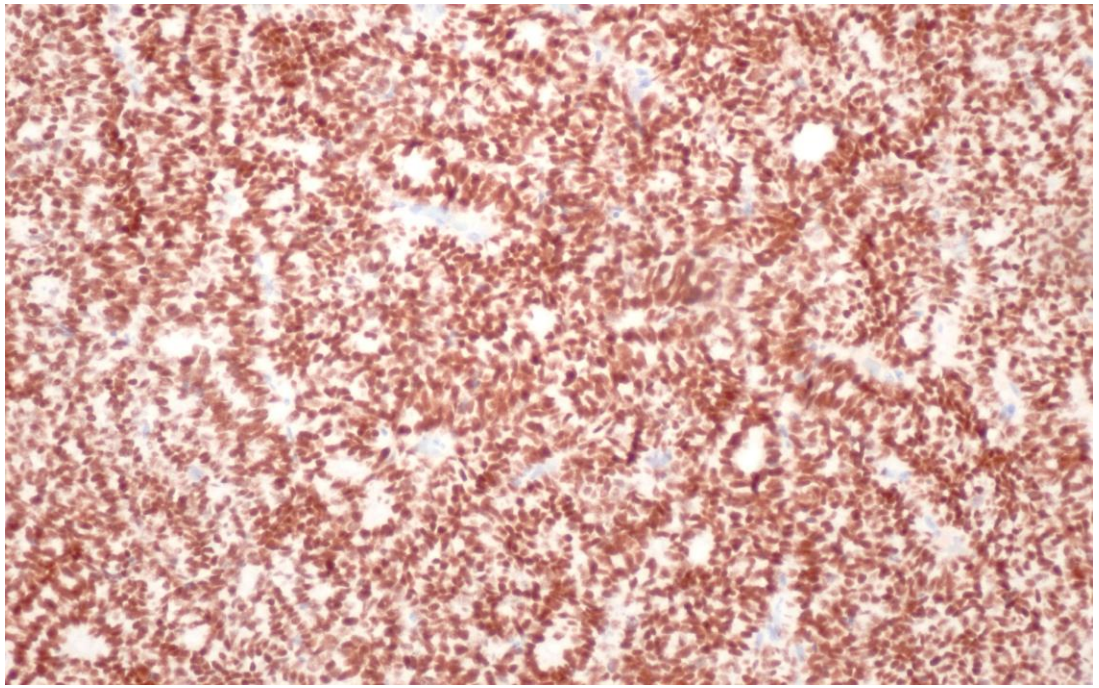
Case 3: Biopsy

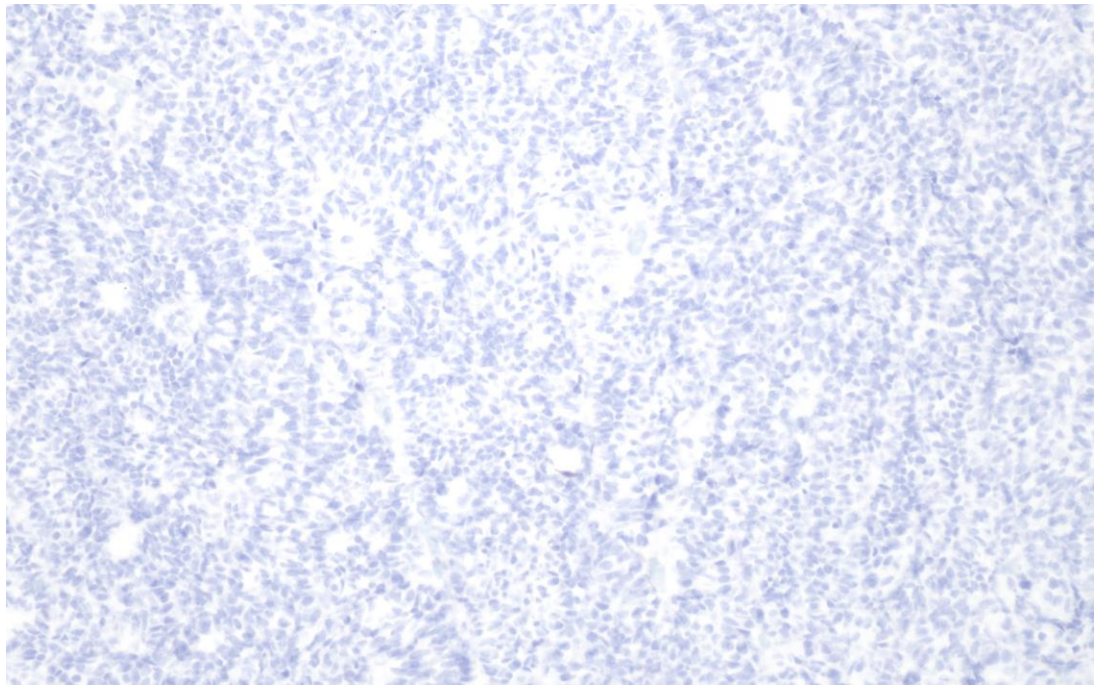


Case 3: Biopsy, ER



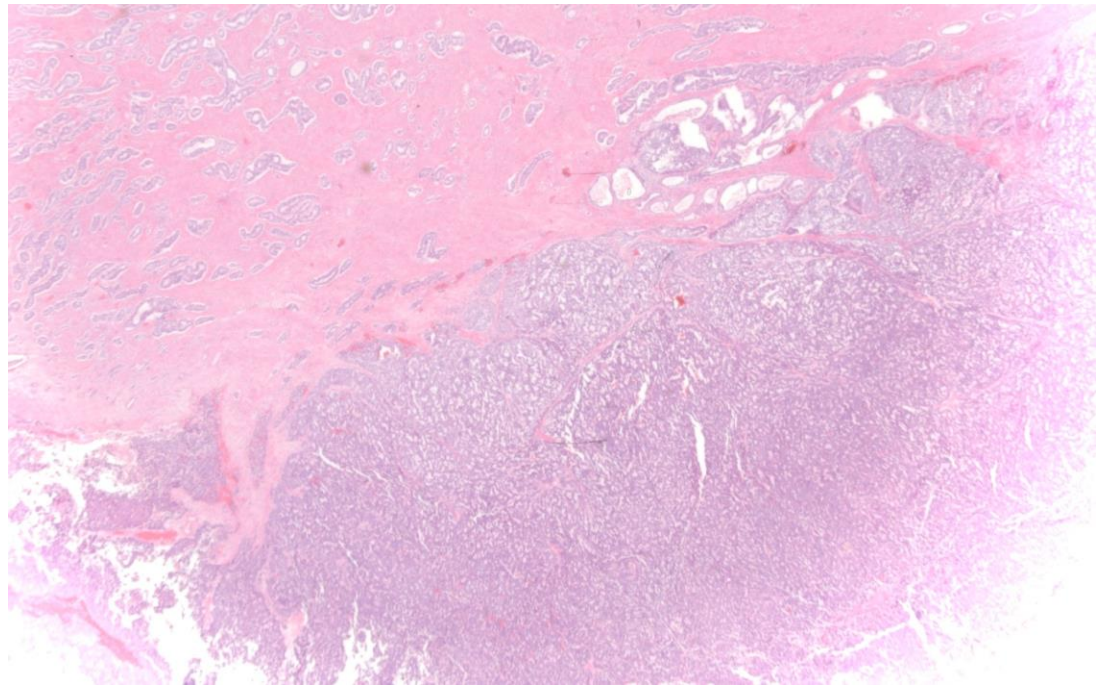
Case 3: Biopsy, GATA3 positive; TTF1 negative

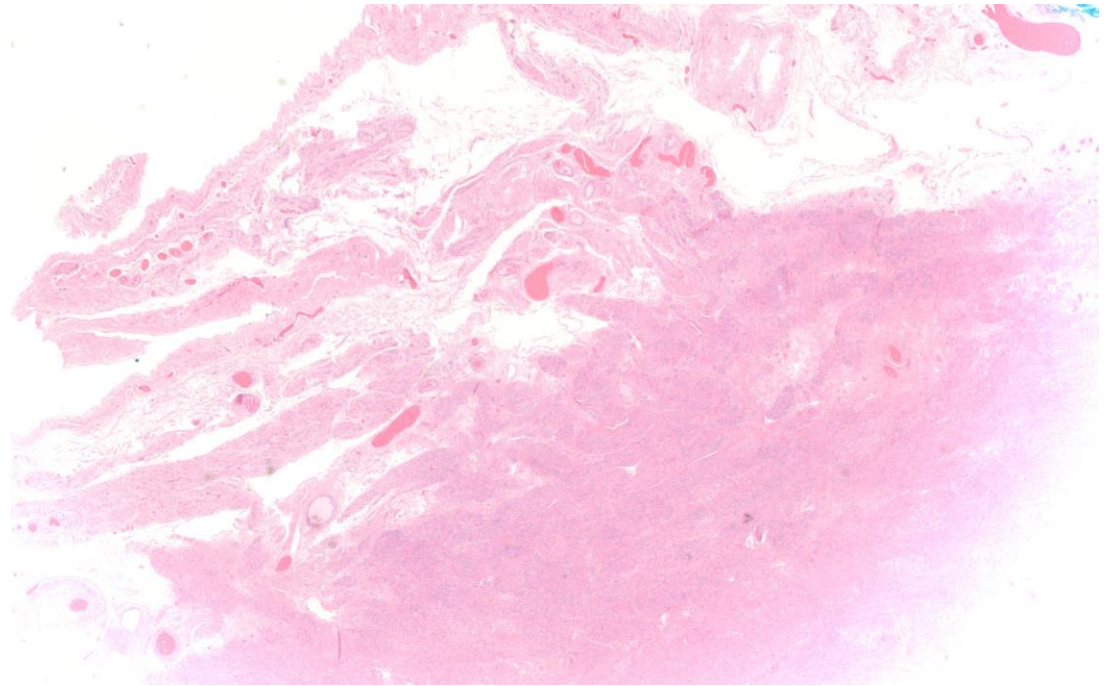




Case 3: Biopsy diagnosis

- High-grade adenocarcinoma, mesonephric-like morphology
- The DD lies between primary cervical mesonephric ca and an endometrial mesonephric-like ca
- Correlation with clinical and imaging findings recommended as these are morphologically indistinguishable





Case 3: Hysterectomy

- Mesonephric-like adenocarcinoma of endometrium
- Invasion of isthmus and cervical stroma
- Focal LVSI prresent
- Negative for mesonephric remnants
- pT2 pN0

- Adjuvant treatment recommended: Chemotherapy and pelvic RT
- Patient declined chemotherapy and agreed to proceed with RT

ER expression in NSMP EC

(Vermij et al. Int J Gynecol Cancer 2021; 31:A89-A90)

Figure 1. Overview of clinicopathological and molecular characteristics of NSMP-EC from PORTEC-3

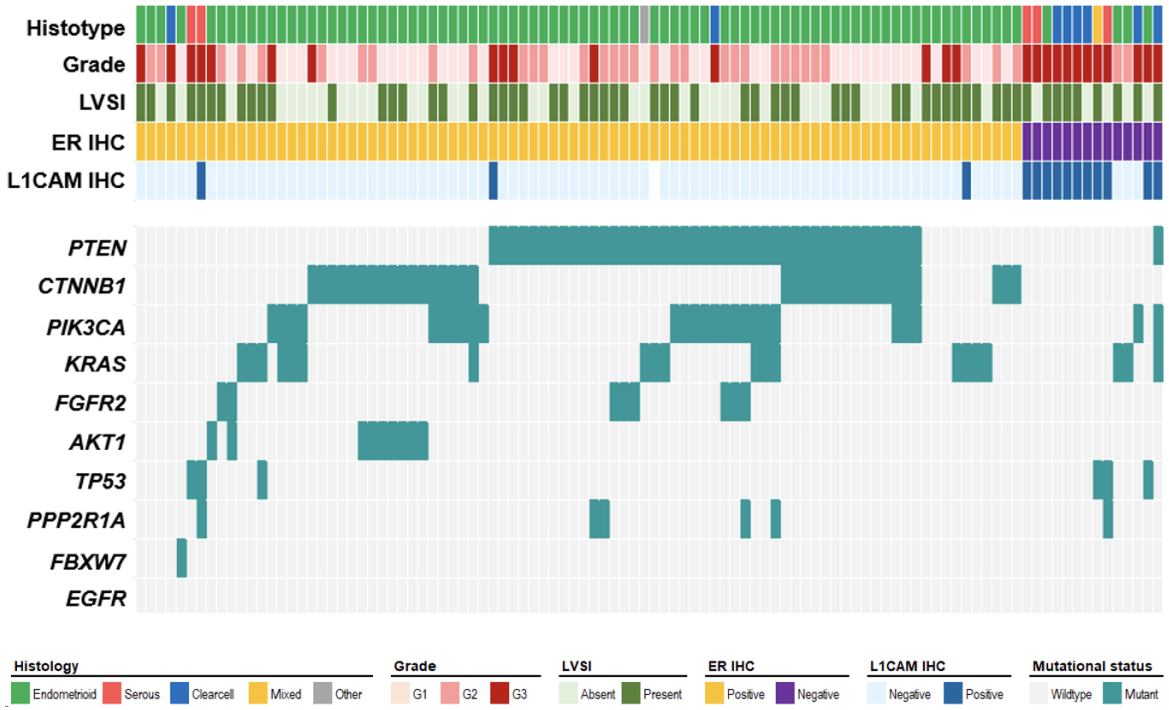
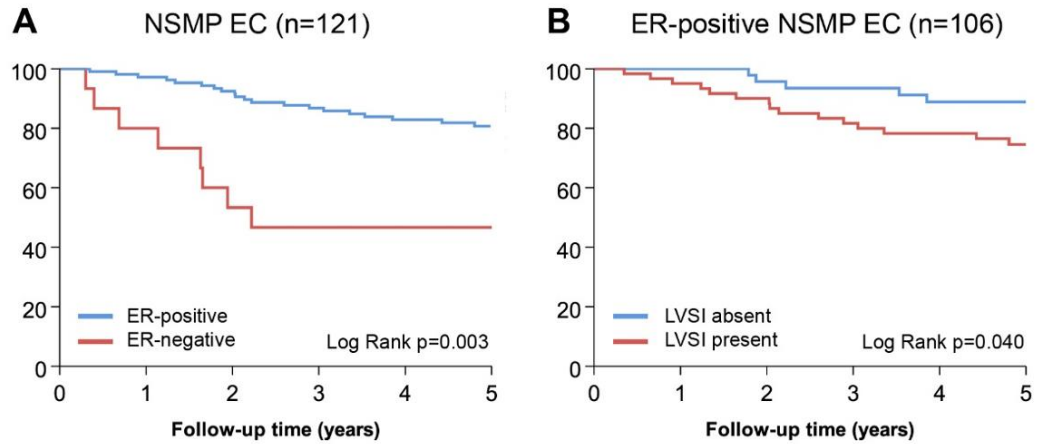


Figure 2. Time to recurrence within NSMP-EC



Kaplan-Meier survival analyses demonstrating the time to recurrence of ER immunohistochemical expression in endometrial cancers (EC) without a specific molecular profile (NSMP) (A) and for the presence of lymphovascular space invasion (LVSI) in ER-positive NSMP-EC (B).

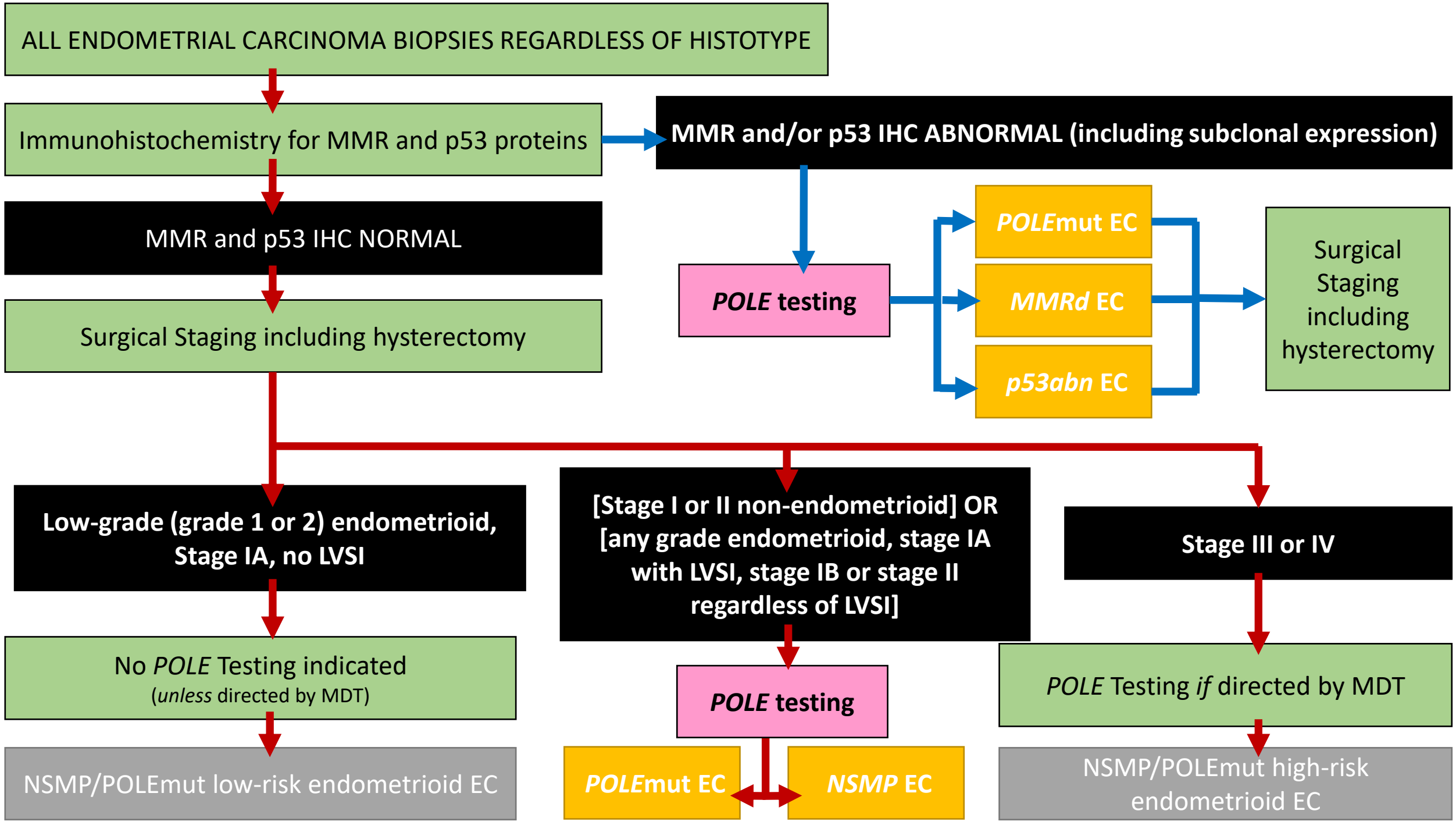
Courtesy of Dr Lisa Vermij

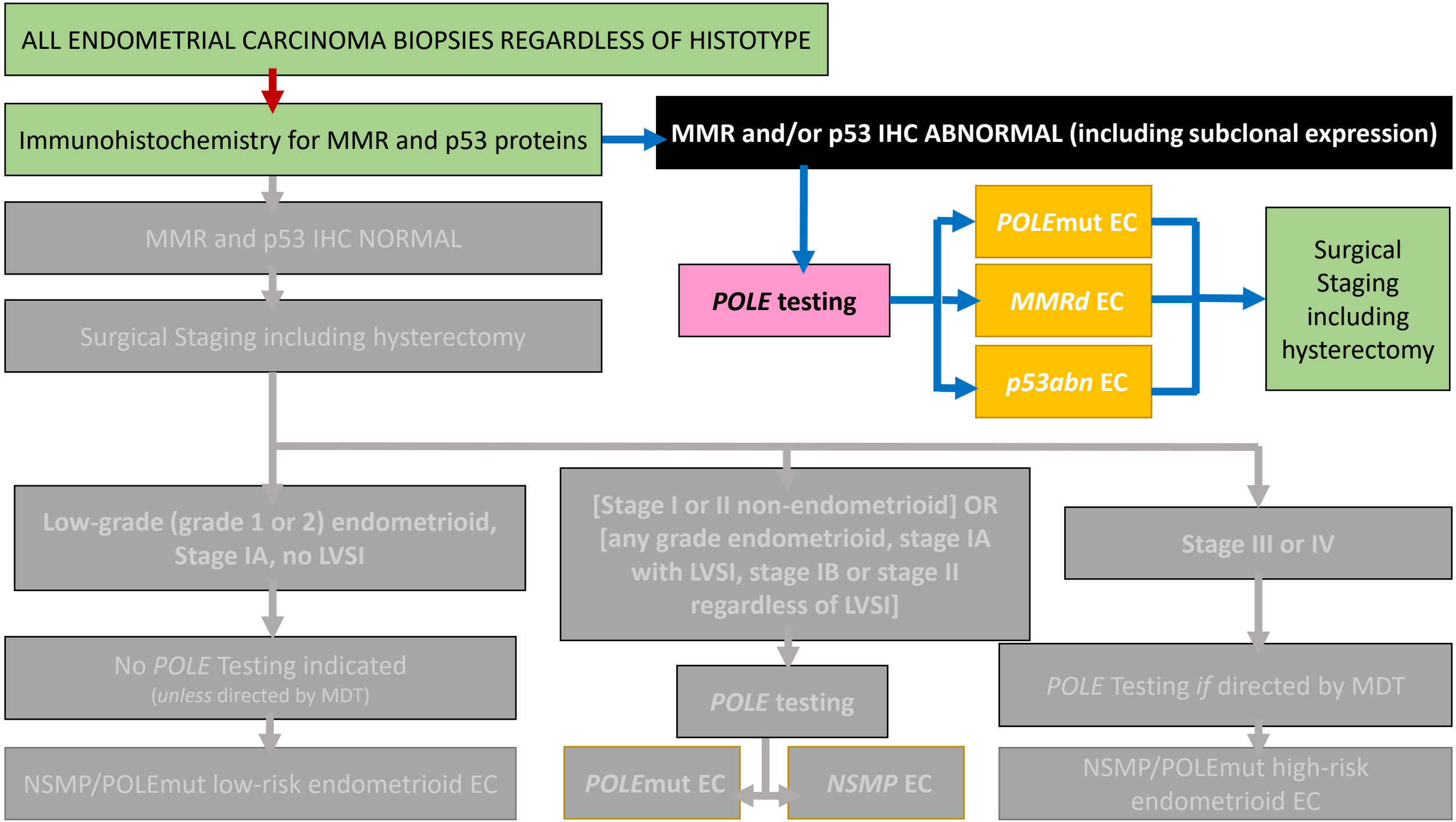
Recommended approach to IHC in endometrial carcinoma

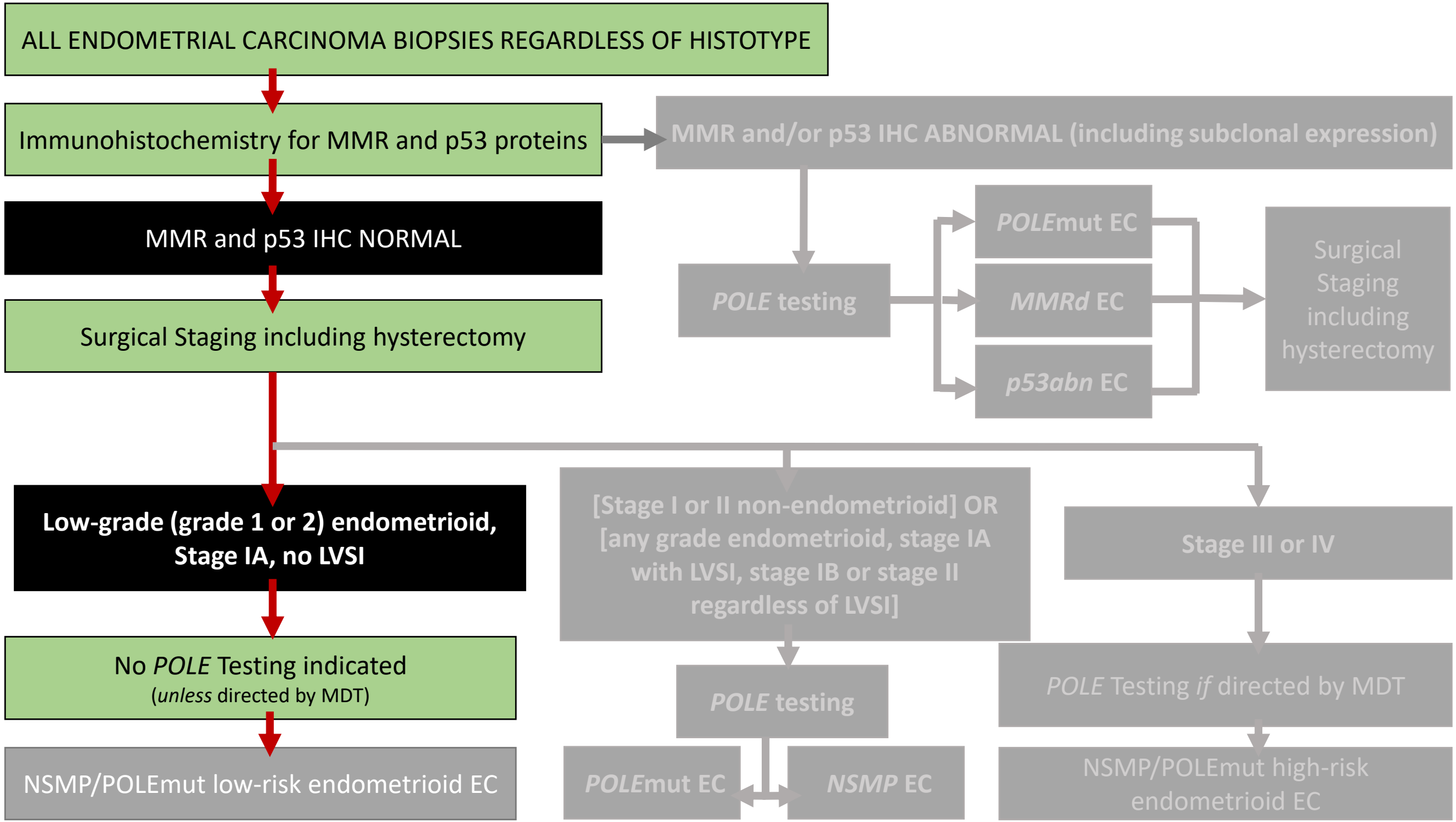
- ER, p53 and MMR IHC on every case, regardless of histotype

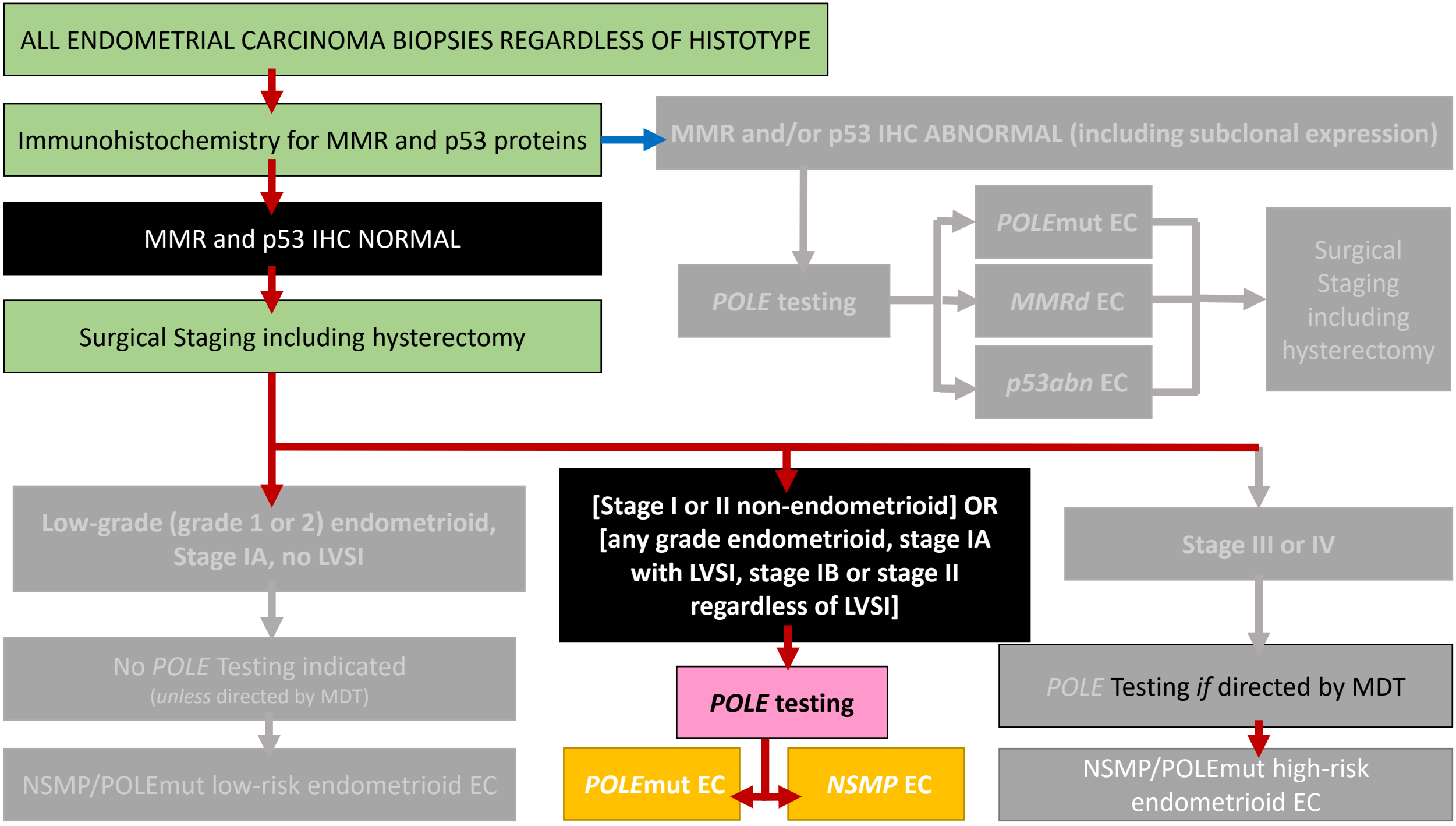
Recommended approach to *POLE* testing in endometrial carcinoma

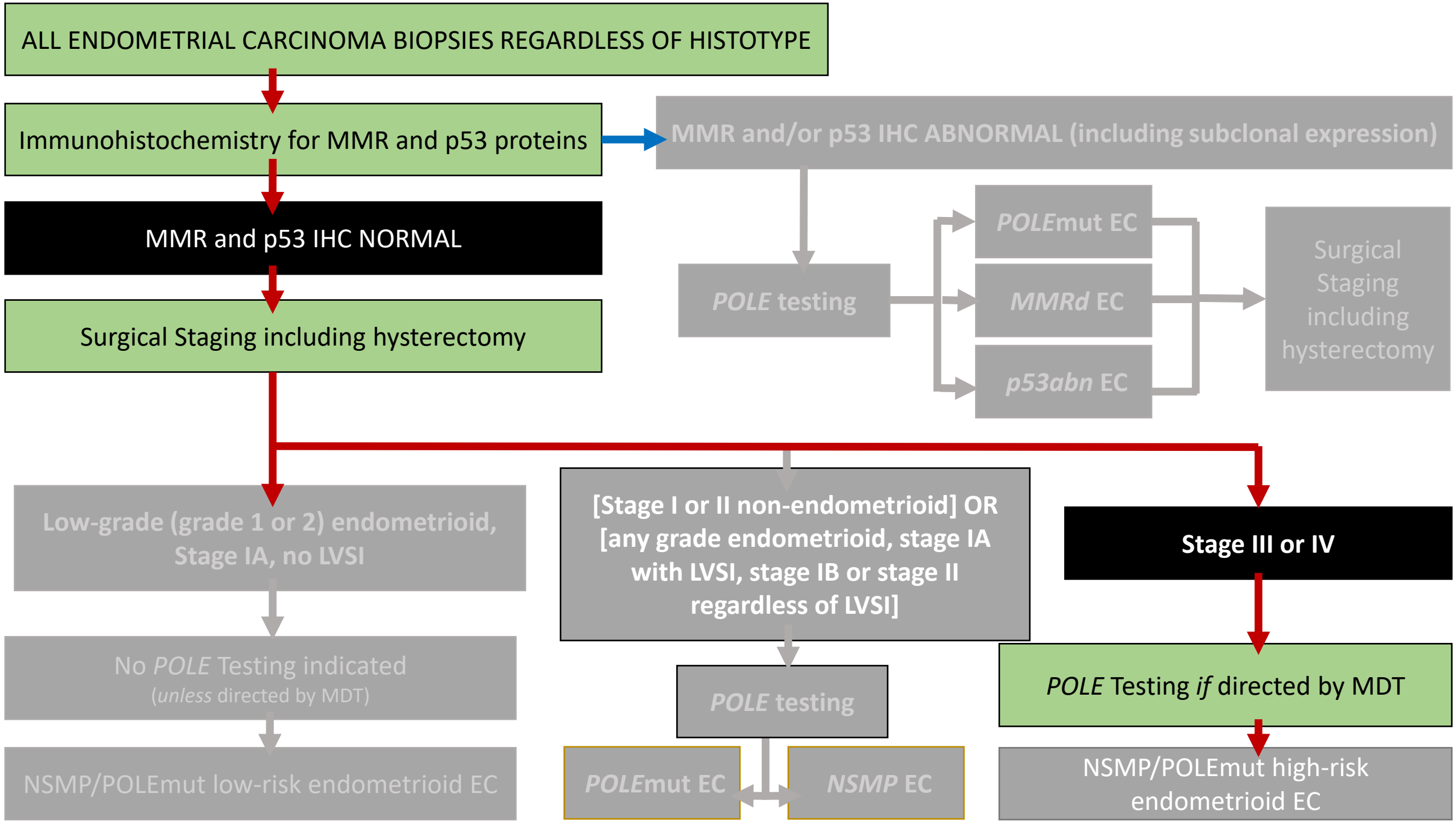
- Successful application by BAGP, supported by BGCS and 2 women's cancer charities
- POLE testing is to be included in NHSE testing directory from April 2022
- Also imminently in Wales (Dr Adam Boyde)


ALL ENDOMETRIAL CARCINOMA BIOPSIES REGARDLESS OF HISTOTYPE
Immunohistochemistry for MMR and p53 proteins
MMR and/or p53 IHC ABNORMAL (including subclonal expression)
MMR and p53 IHC NORMAL
POLE testing
POLEmut EC
MMRd EC
p53abn EC
Surgical Staging including hysterectomy
Surgical Staging including hysterectomy
Low-grade (grade 1 or 2) endometrioid, Stage IA, no LVSI
[Stage I or II non-endometrioid] OR [any grade endometrioid, stage IA with LVSI, stage IB or stage II regardless of LVSI]
Stage III or IV
No POLE Testing indicated (unless directed by MDT)
POLE testing
POLE Testing if directed by MDT
NSMP/POLEmut low-risk endometrioid EC
POLEmut EC
NSMP EC
NSMP/POLEmut high-risk endometrioid EC


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POLE testing
POLE Testing if directed by MDT
NSMP/POLEmut low-risk endometrioid EC
POLEmut EC
NSMP EC
NSMP/POLEmut high-risk endometrioid EC

Conclusions

- Accurate assessment of histotype, grade (endometrioid EC), stage and LVSI remain fundamental to correct patient management

- Molecular classification is an adjunct to classical histopathology, not a substitute

- Molecular classification impacts on therapeutic decisions: whether to give and what to give (conventional and targeted therapies)

- Universal testing for ER, p53 and MMR with a selective protocol for *POLE* testing is recommended within the UK

ELECTRA

Thank you!

b+tlc BARTS CHARITY
Funding extraordinary healthcare

NHS
Barts Health
NHS Trust

Vancouver CoastalHealth

UBC THE UNIVERSITY OF BRITISH COLUMBIA

The British Association of Gynaecological Pathologists

Trans PORTEC

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