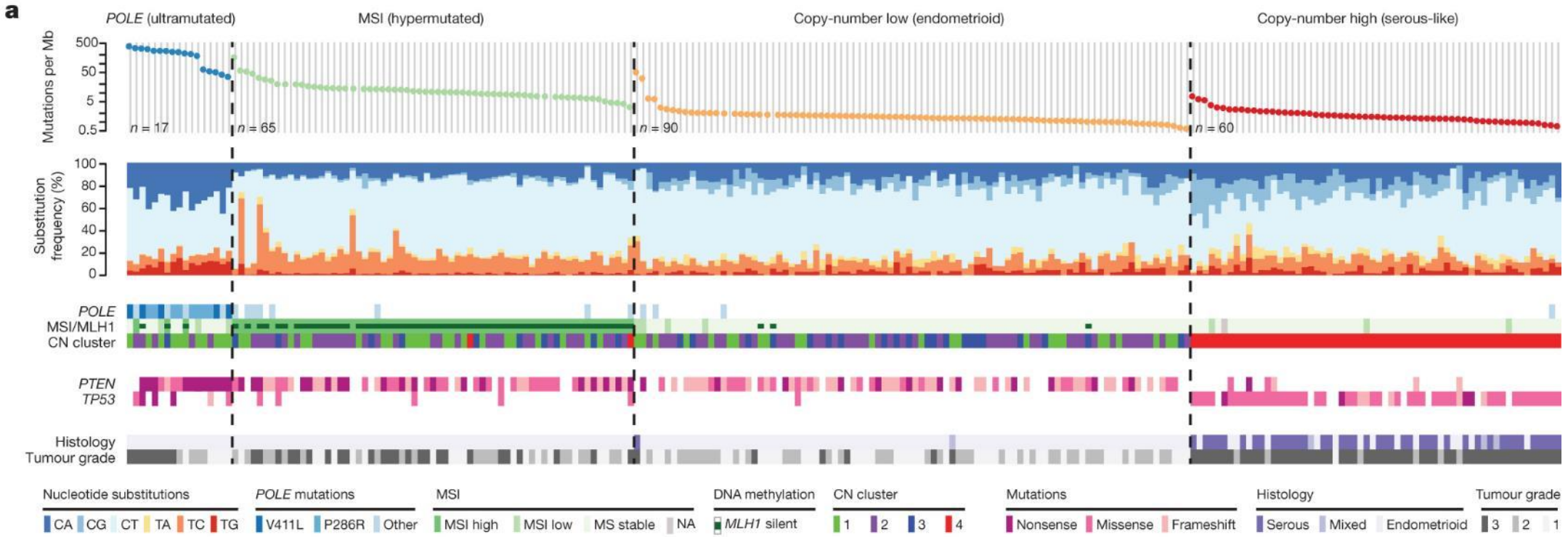
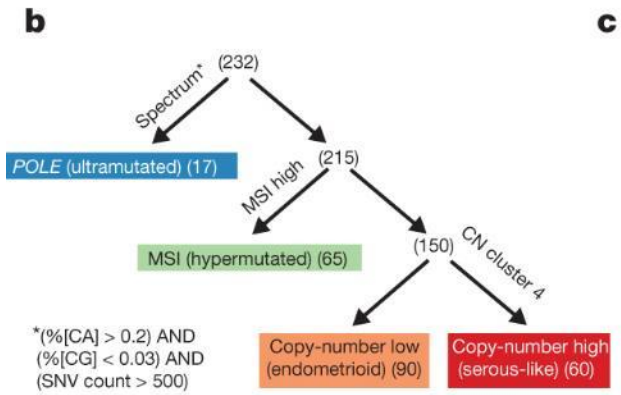
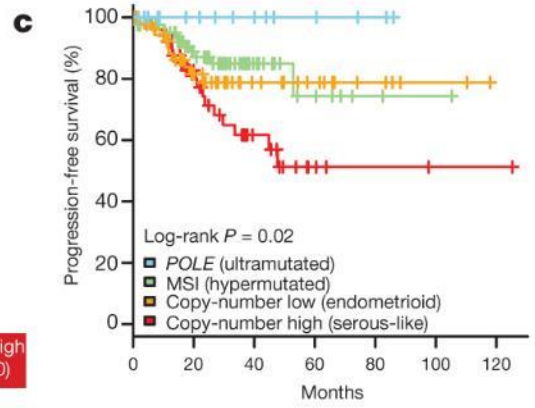
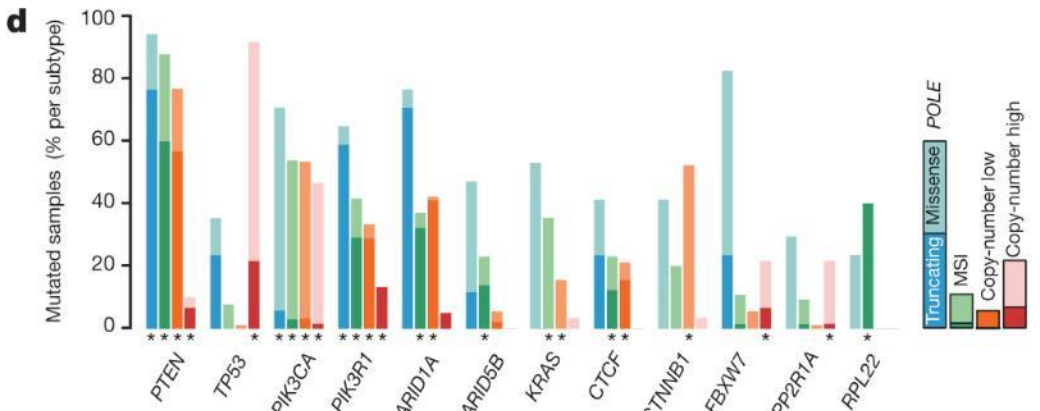
Morphologic Features and Molecular Classification of Endometrial Carcinoma

Robert Soslow, MD









Nature

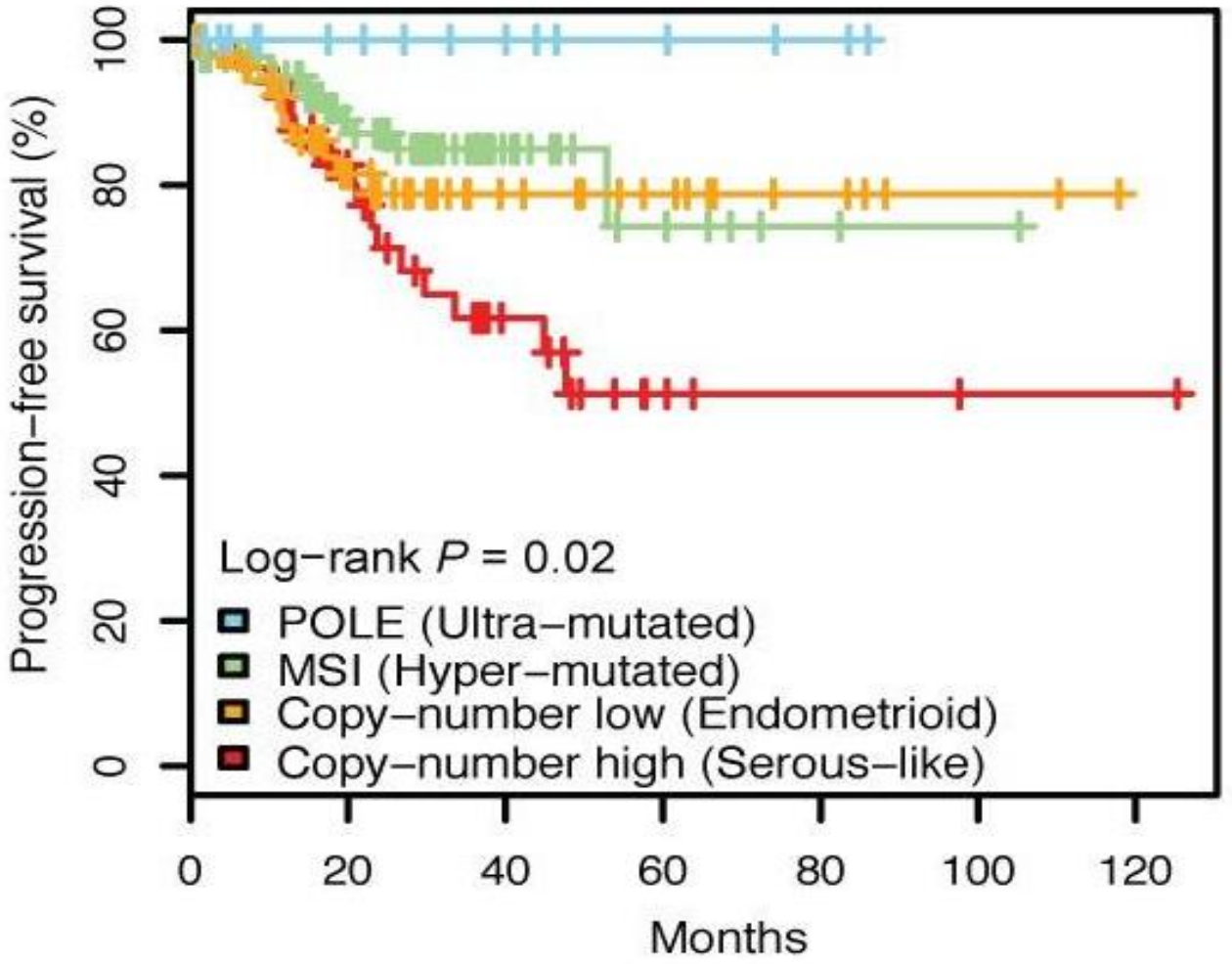
G Getz *et al. Nature* 2013

Molecular classification of endometrial carcinomas

- POLE:
  - ***POLE* exonuclease hotspot mutation**
- MSI-H:
  - **Defective MMR or MSI-H, no *POLE* mutation**
- NSMP/CN-L:
  - **No *POLE* mutation or defective MMR or aberrant p53**
- CN-H/serous-like:
  - **Aberrant p53 expression without *POLE* mutation or defective MMR**

Advantages of molecular classification

- More precise prognosis
- More precise diagnosis
- Therapeutic prediction
- Lynch syndrome risk stratification



G Getz *et al. Nature* 2013

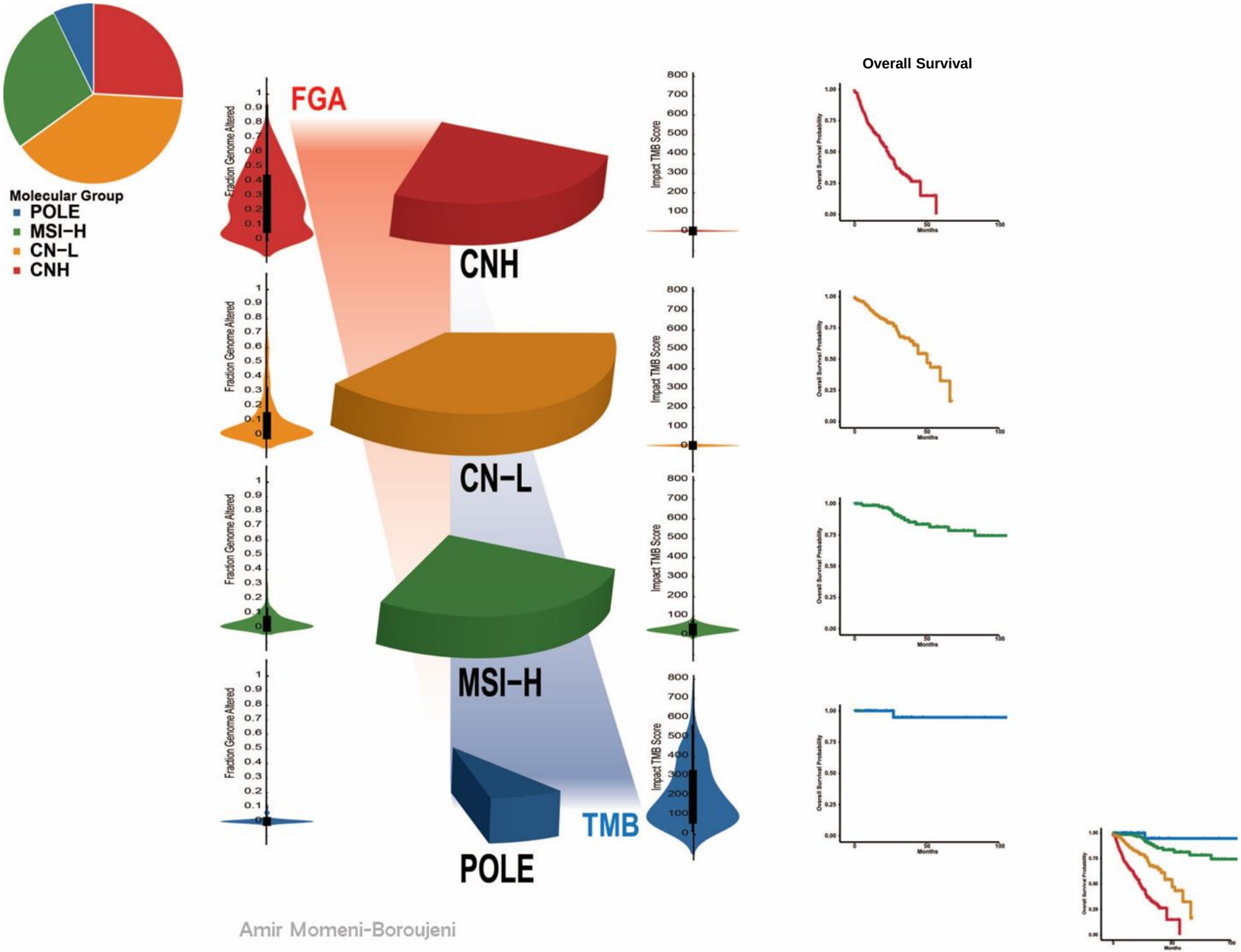
TABLE 1 2023 FIGO staging of cancer of the endometrium.[a,b]

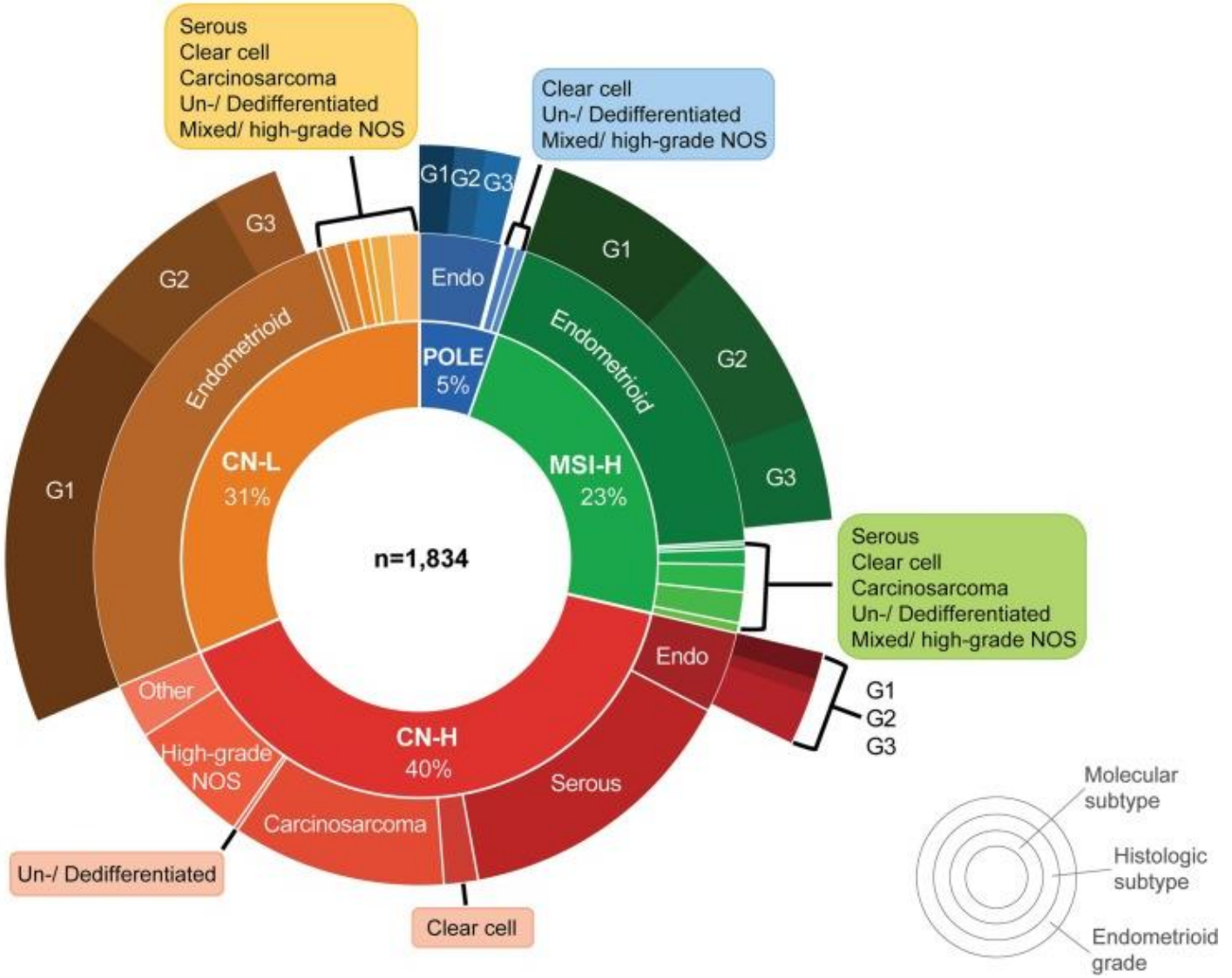
Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement

Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

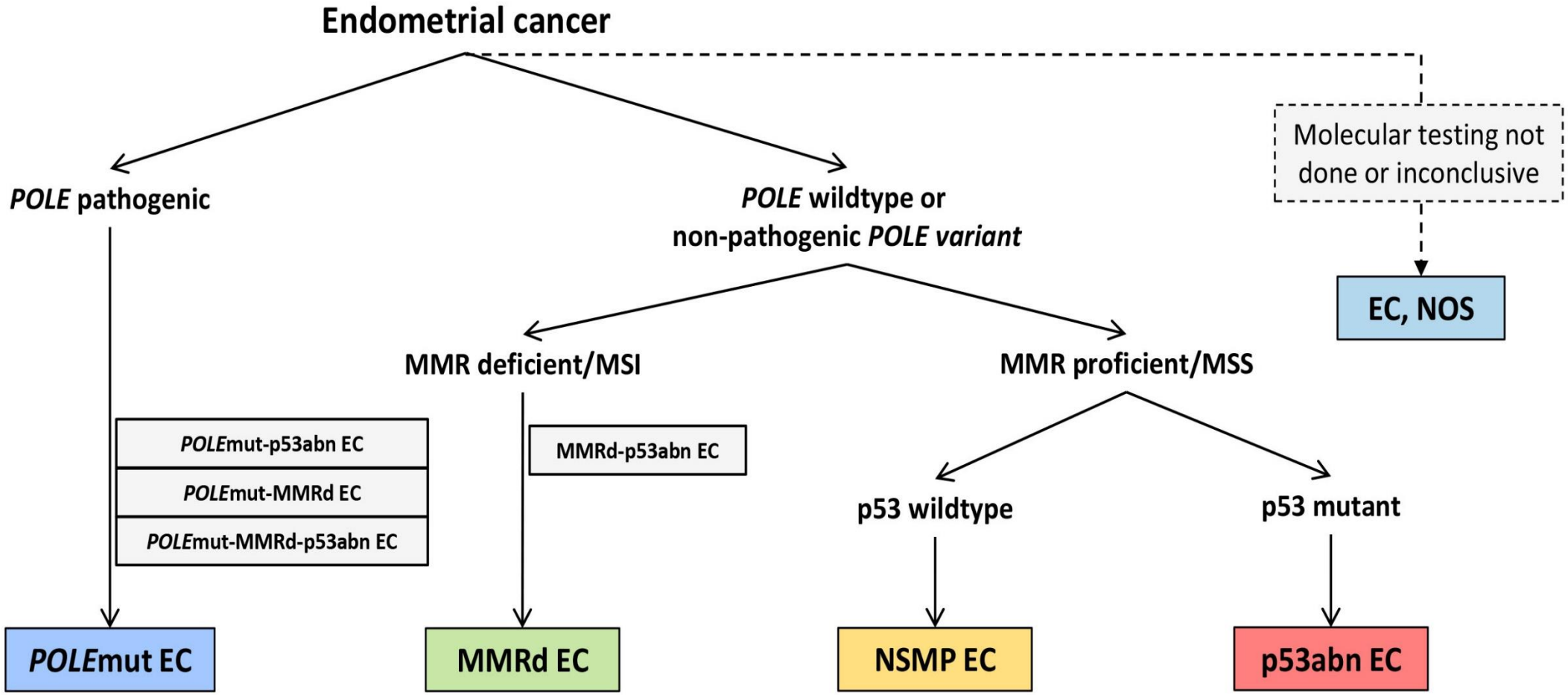
ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up *Ann Oncol*. 2022


Molecular Group
POLE
MSI−H
CN−L
CNH
FGA
CNH
CN−L
MSI−H
TMB
POLE
Fraction Genome Altered
Impact TMB Score
Overall Survival
Overall Survival Probability
Months
Amir Momeni-Boroujeni

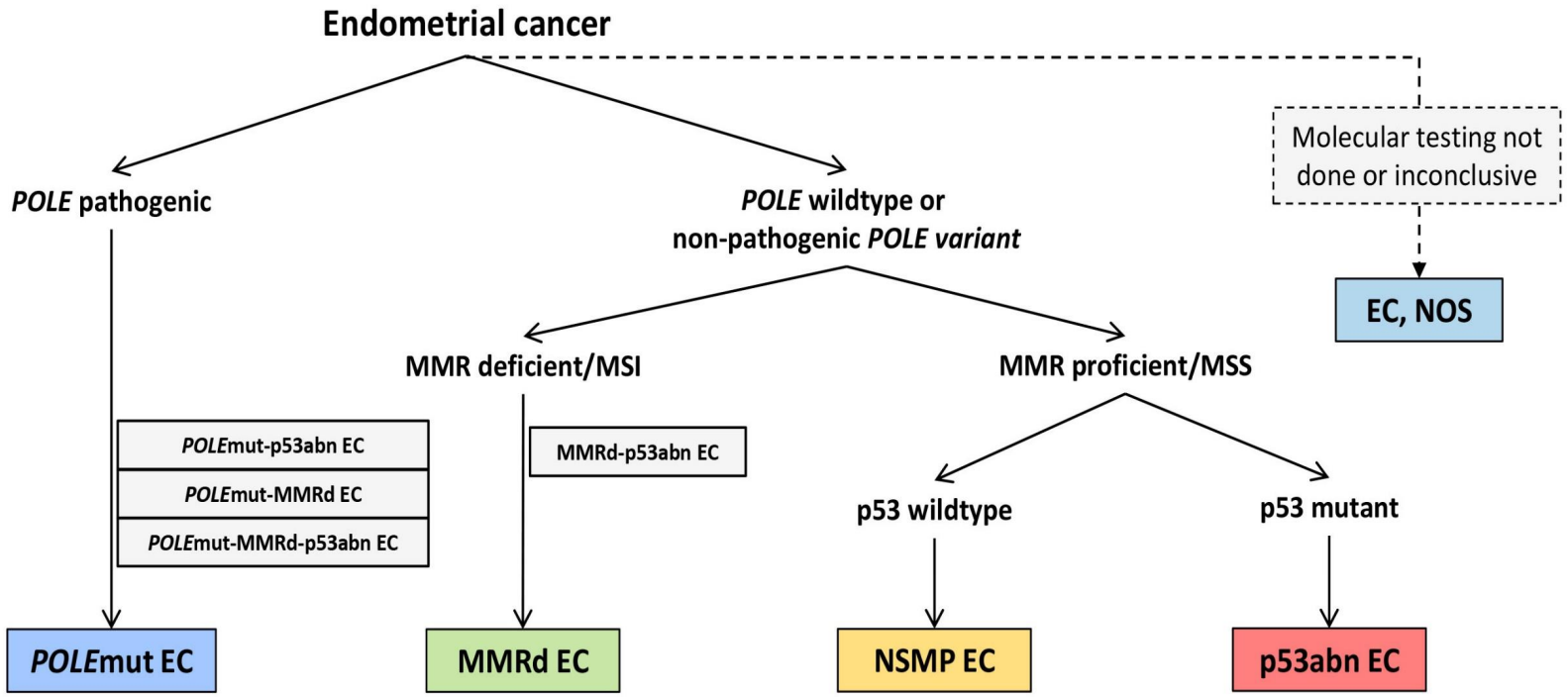


Rios-Doria, E, *et al., Gynecologic Oncology* 2023

Harnessing genomic data for diagnosis, prognostication, therapeutic prediction (PROMISE algorithm)



Courtesy of Tjalling Bosse MD

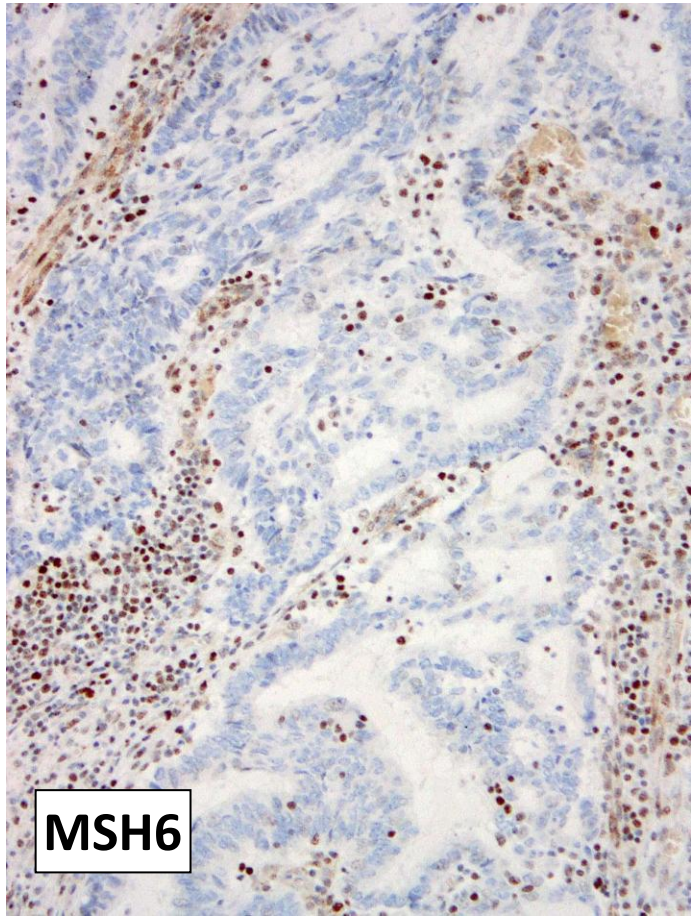


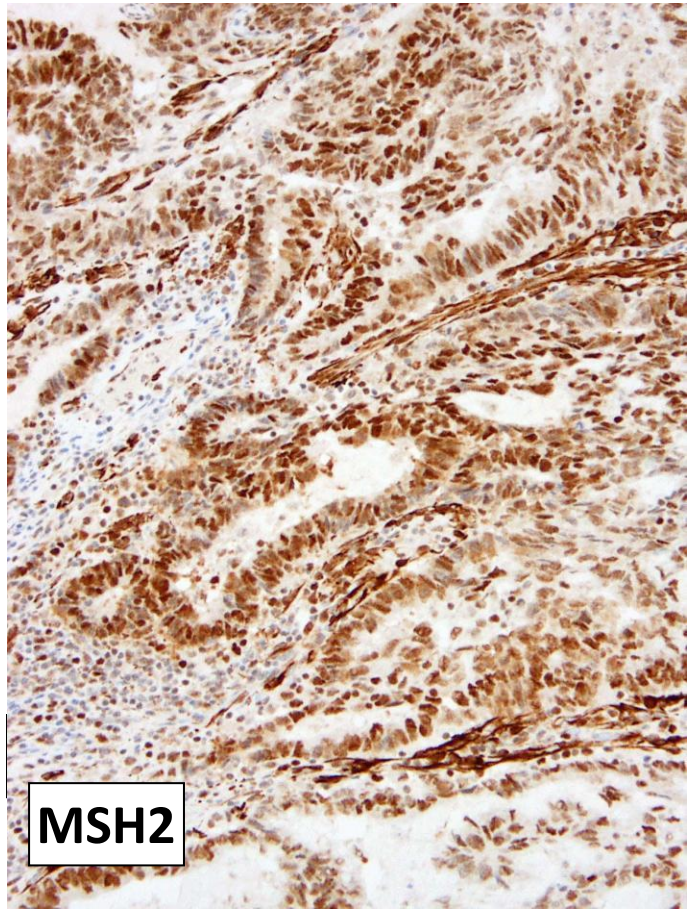
Courtesy of Tjalling Bosse MD

Deep Learning/AI may predict molecular subtypes

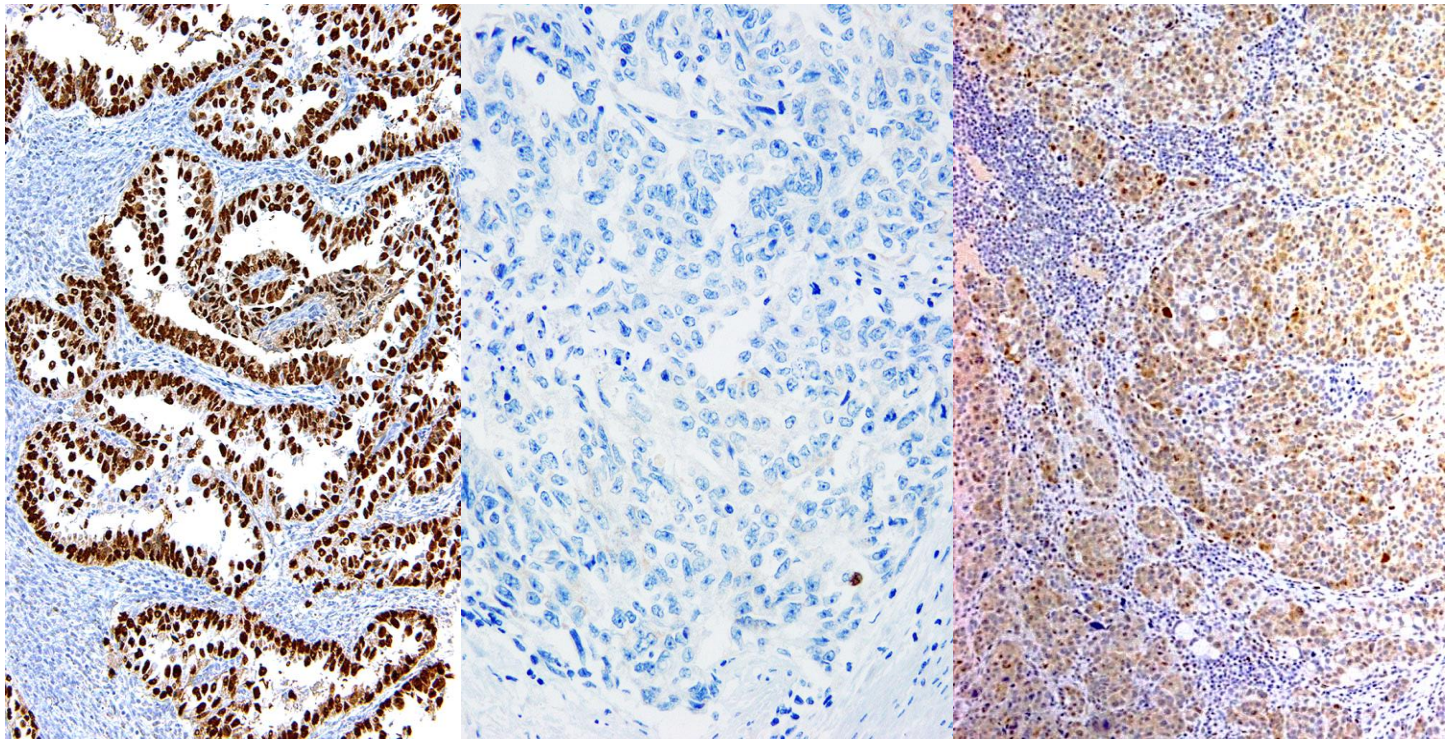
Lancet Digit Health 2023 Feb;5(2):e71-e82

MMR deficiency

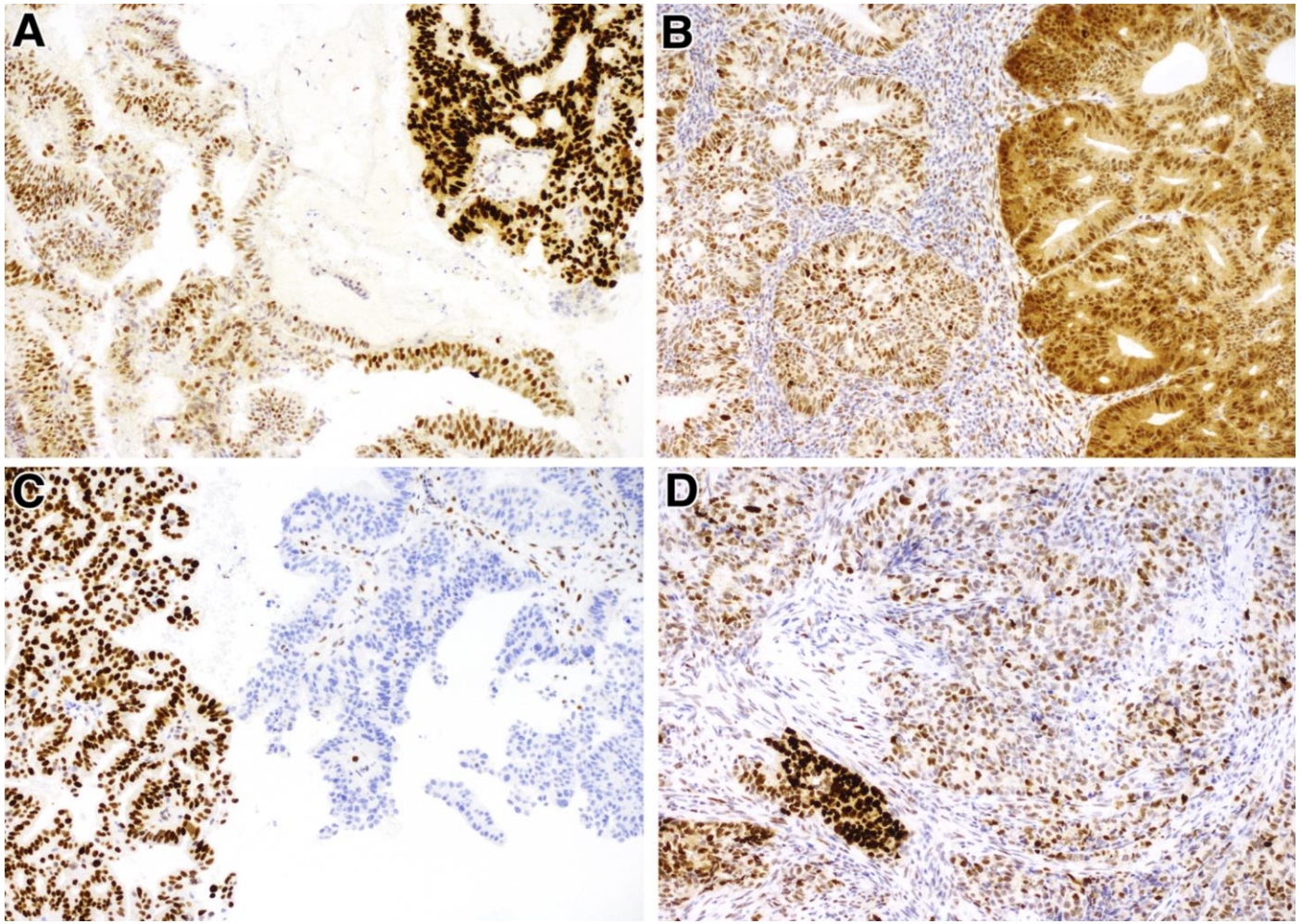




Aberrant p53 staining



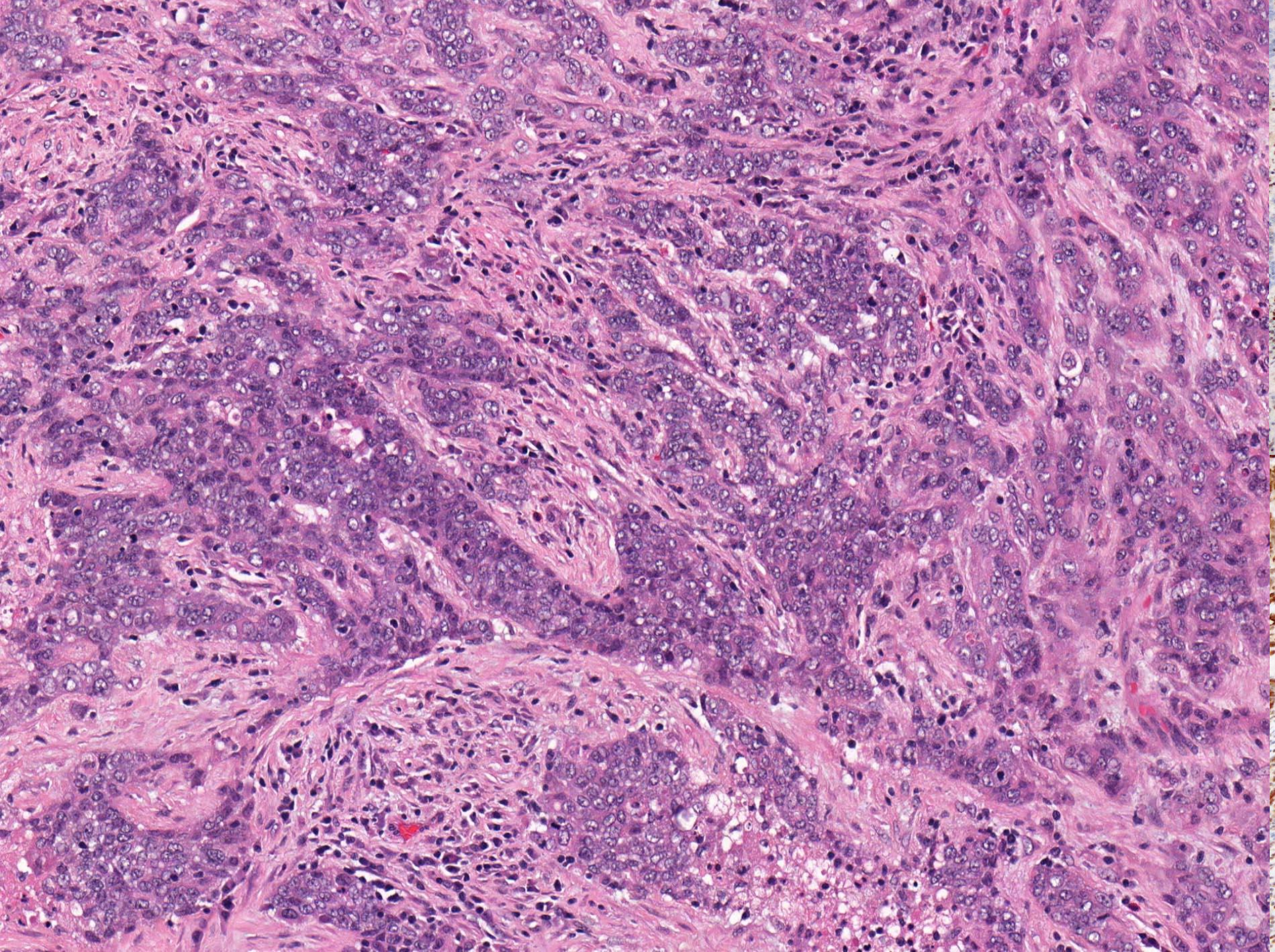
Subclonal staining

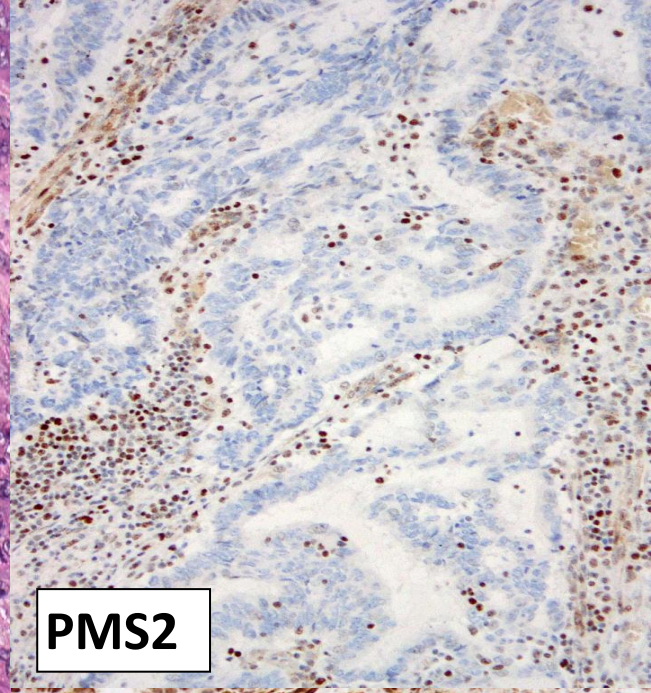


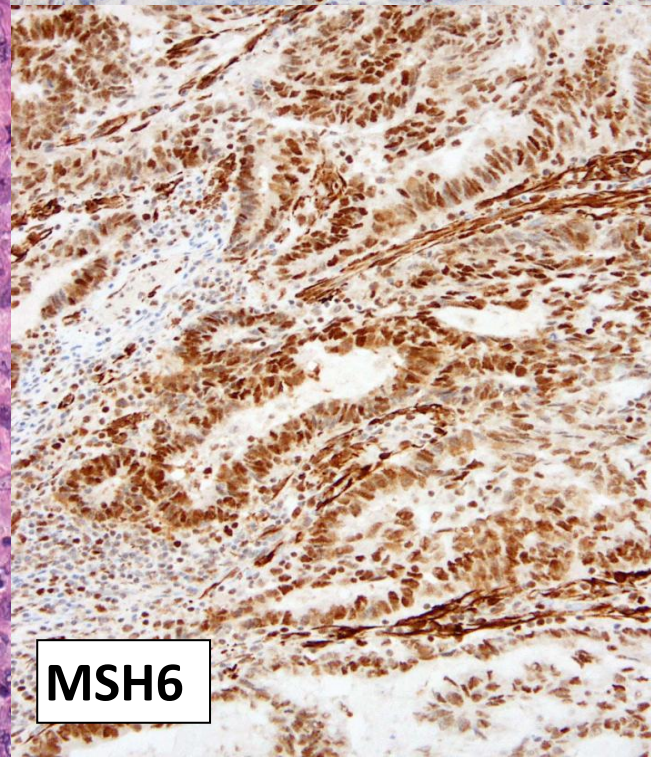
J Pathol: 3, 336-345

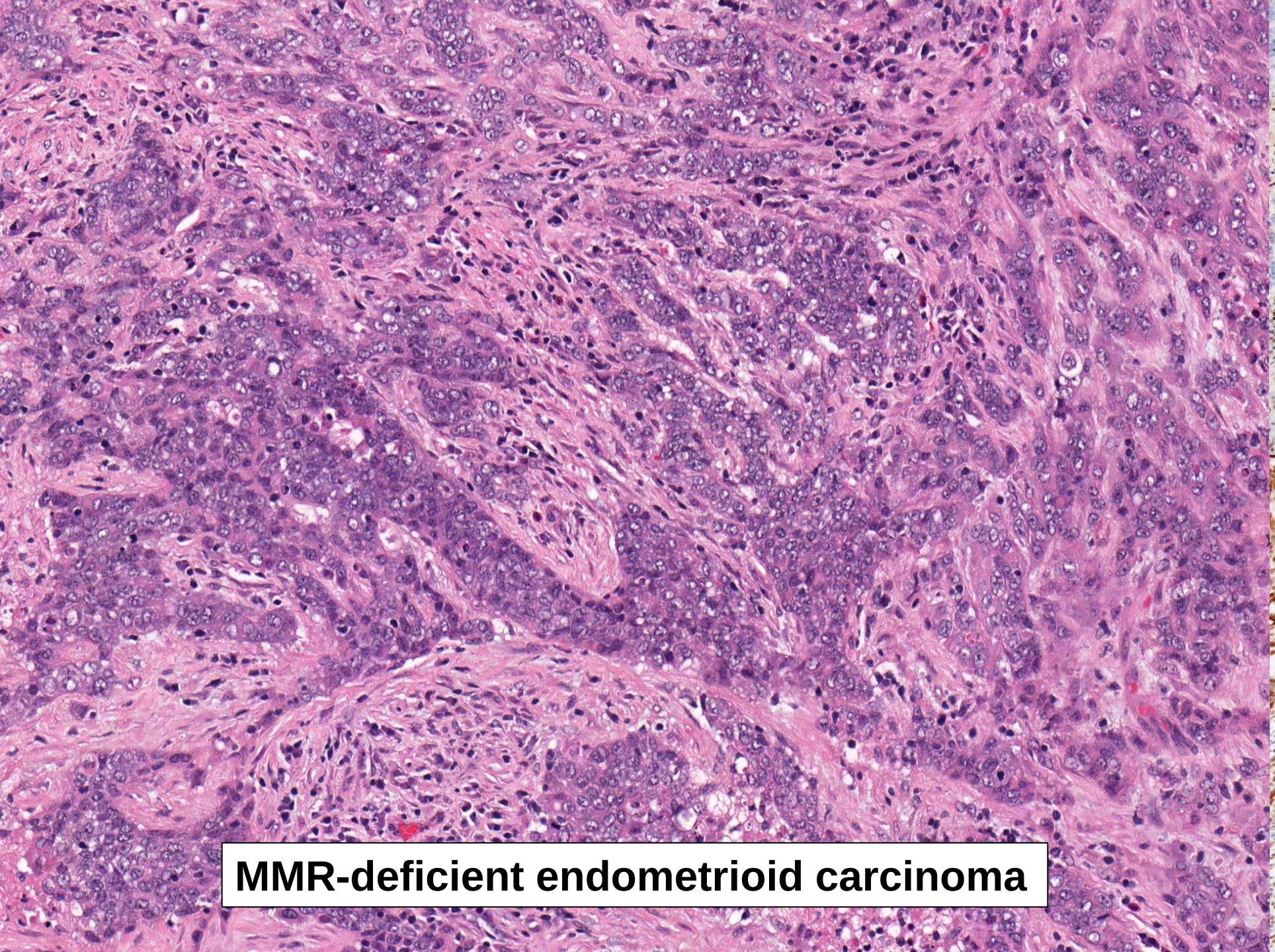
Case presentation

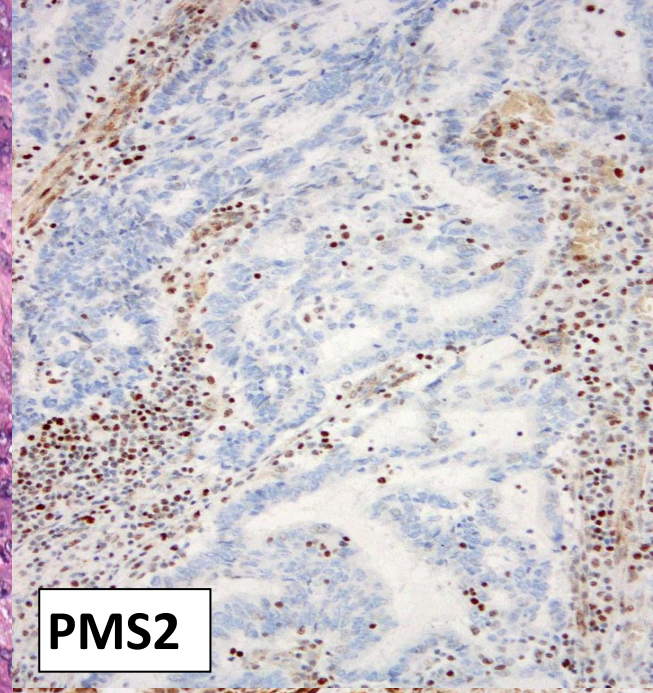
- 65 year-old patient
- FIGO grade 3 endometrioid carcinoma
- FIGO stage IIC (2023) and FIGO stage IA (2009)

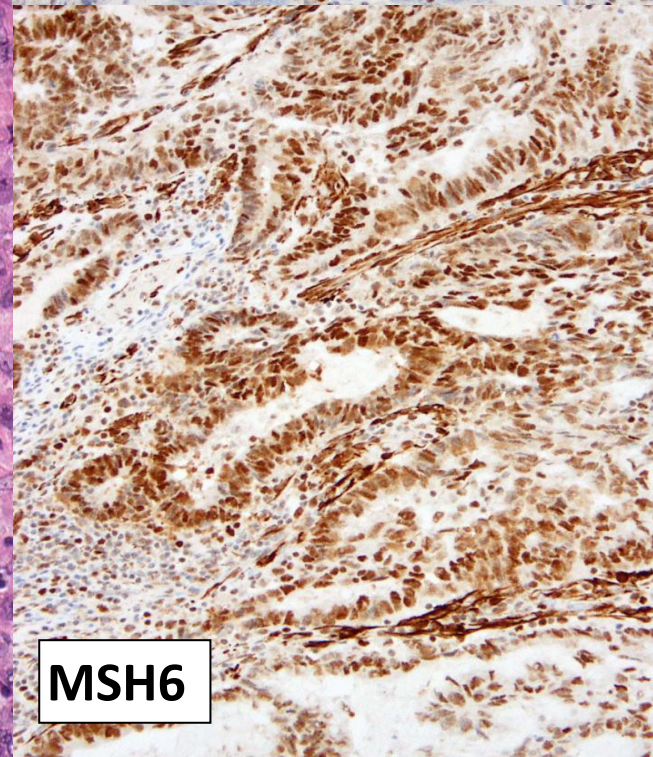



PMS2

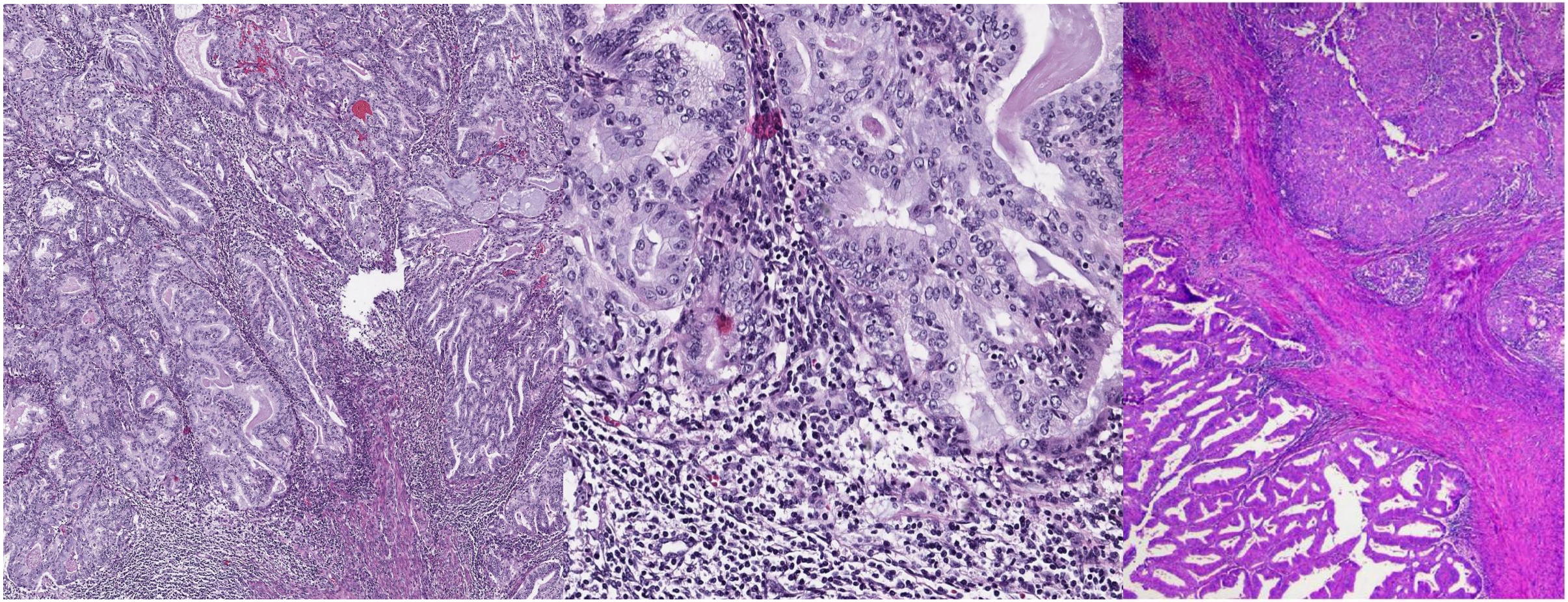

MSH6


MMR-deficient endometrioid carcinoma

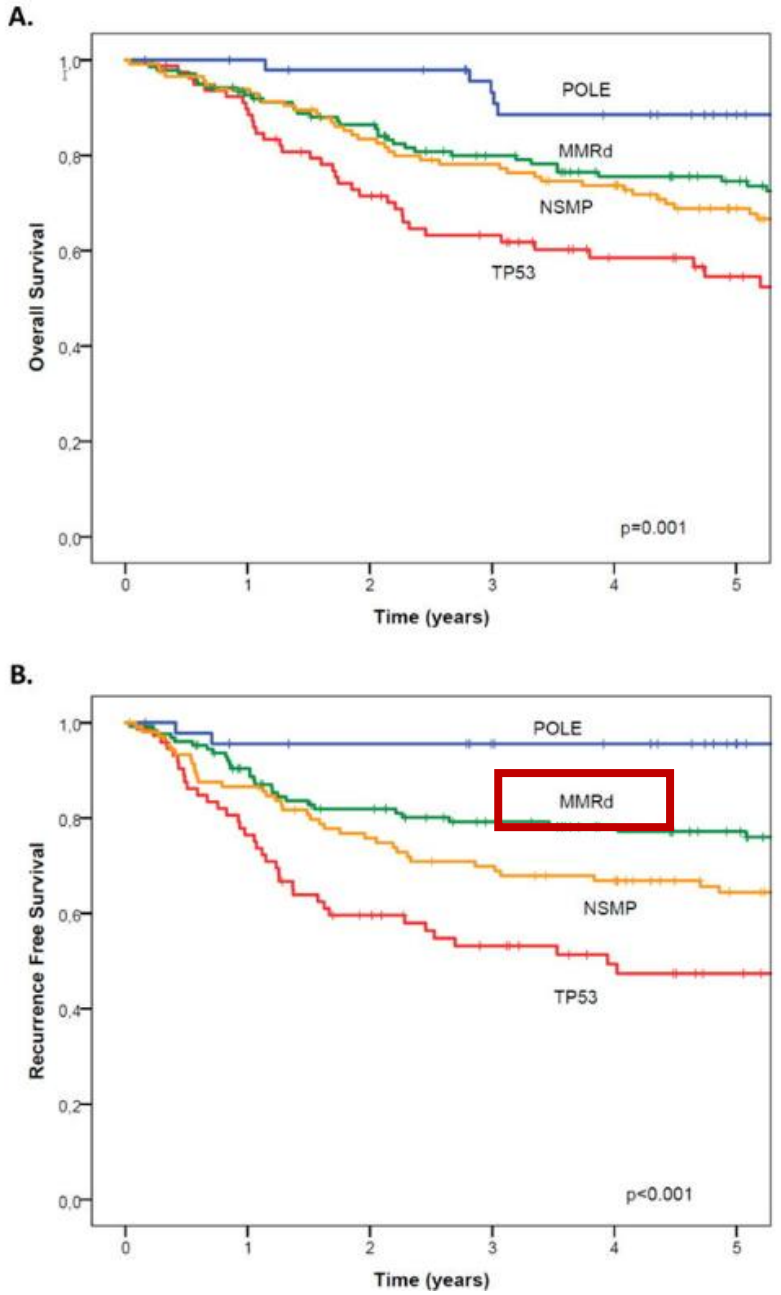

PMS2


MSH6

Common features of MMR deficient (MMRd) endometrial carcinomas

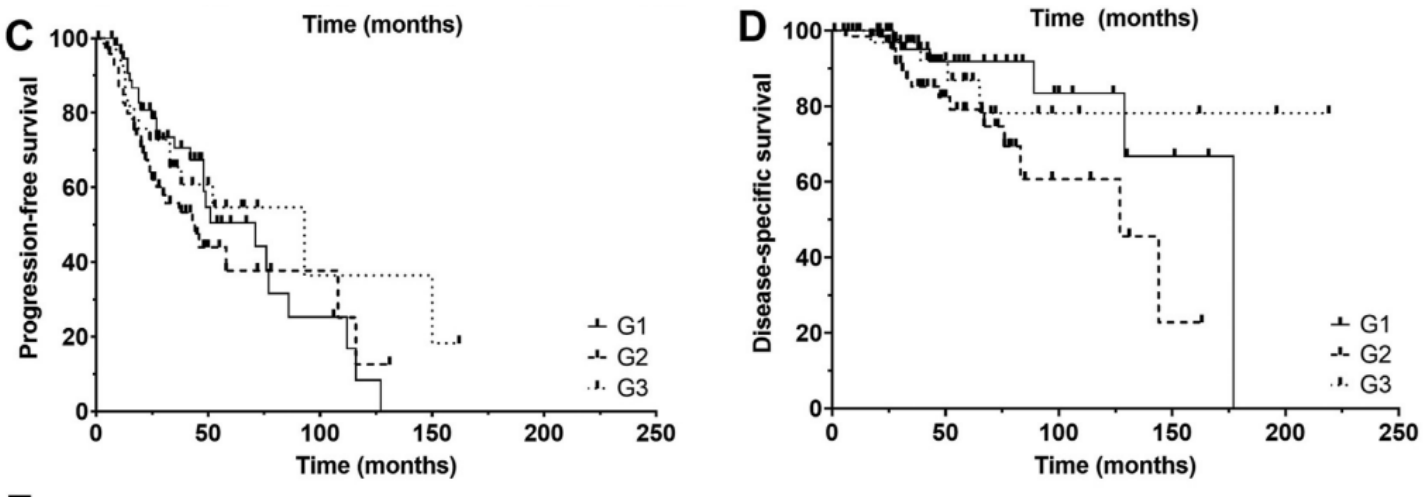


FIGO G3 endometrioid



Bosse T, *et al*. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. *Am J Surg Pathol* (2018)

Grade and survivals in MMRd

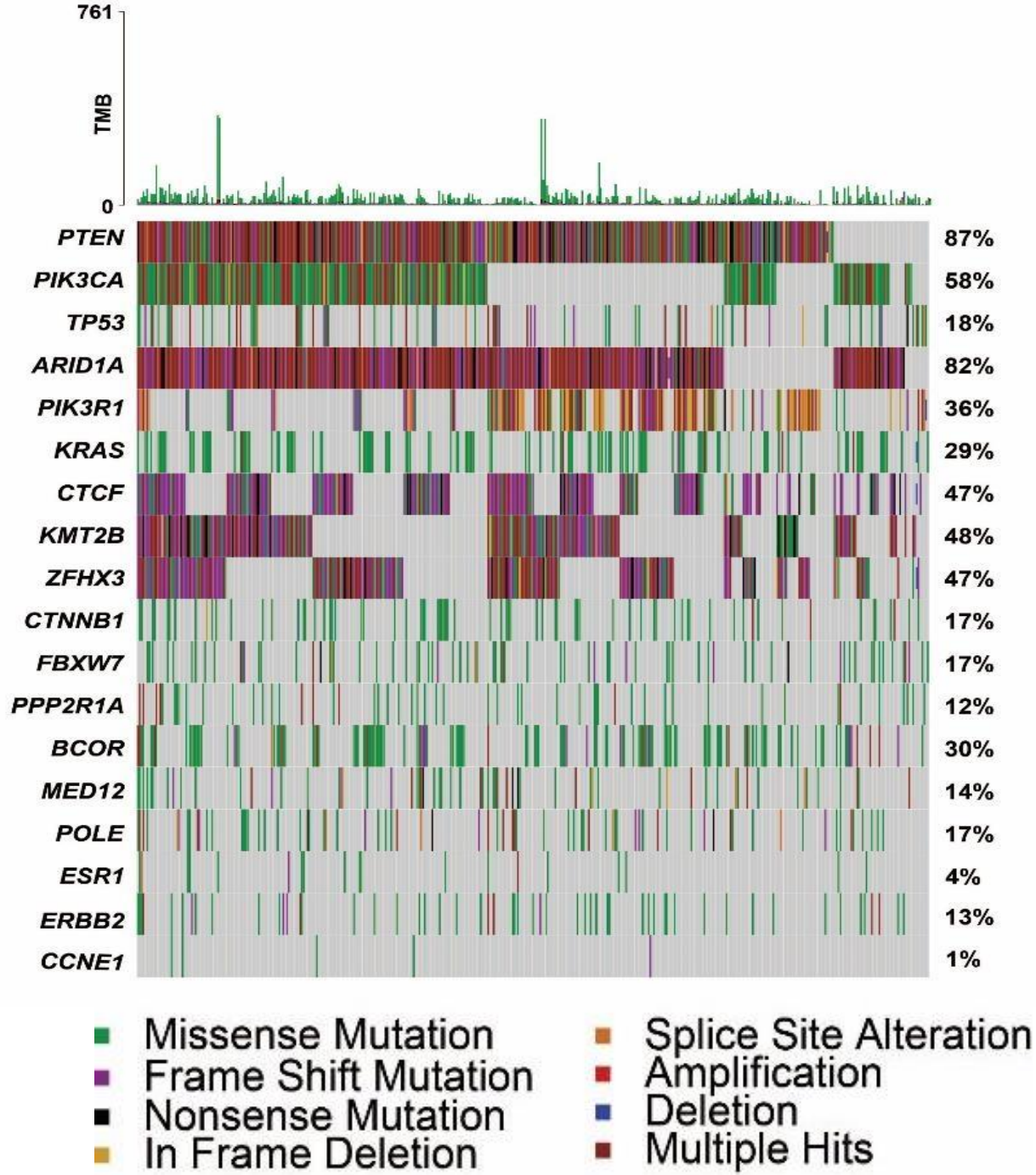


PMID: 37268062

Summary	61 mutations, no copy number alterations, no structural variants detected. 3 alterations have OncoKB treatment interpretations.
MSI Status	MICROSATELLITE INSTABILITY-HIGH (MSI-H). See MSI note below.[β]
Tumor Mutation Burden	The estimated tumor mutation burden (TMB) for this sample is 53.5 mutations per megabase (mt/Mb). The median TMB assessed by MSK-IMPACT for all patients is 3.9 mt/Mb and for patients with Endometrial Cancer is 6.1 mt/Mb as of the date this report was issued.[γ]

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Mutations				
BRCA2	Frameshift Deletion	S234Pfs*7 *(c.700del)*	exon 9	MAF: 42.3% a
PTCH1	Frameshift Deletion	V994* *(c.2979del)*	exon 18	MAF: 39.6%
PTEN	Splicing Mutation	X85_splice *(c.253+1G>A)*	exon 4	MAF: 42.9%
PTEN	Nonsense Mutation	Q298* *(c.892C>T)*	exon 8	MAF: 24.0%
CTNNB1	Missense Mutation	T41A *(c.121A>G)*	exon 3	MAF: 45.2%
KDM5C	Missense Mutation	R159H *(c.476G>A)*	exon 4	MAF: 39.5%
PIK3R1	Missense Mutation	K379E *(c.1135A>G)*	exon 10	MAF: 42.4%
RRAS2	Missense Mutation	Q72L *(c.215A>T)*	exon 3	MAF: 40.6%
SOX17	Missense Mutation	A96G *(c.287C>G)*	exon 1	MAF: 42.4%
ARID1A	Frameshift Deletion	P109Afs*6 *(c.325_329del)*	exon 1	MAF: 37.7%
AXIN2	Frameshift Deletion	G665Afs*24 *(c.1994del)*	exon 8	MAF: 38.9%
CTCF	Frameshift Deletion	V100* *(c.298_301del)*	exon 3	MAF: 40.5%
EPHA3	Frameshift Deletion	M847Wfs*10 *(c.2538del)*	exon 15	MAF: 7.0%
JAK1	Frameshift Deletion	K860Nfs*16 *(c.2580del)*	exon 19	MAF: 79.6%
KMT2D	Frameshift Deletion	L656Cfs*274 *(c.1966del)*	exon 10	MAF: 32.2%
KMT2D	Frameshift Deletion	A2119Lfs*25 *(c.6354del)*	exon 31	MAF: 41.4%
MSH3	Frameshift Deletion	K383Rfs*32 *(c.1148del)*	exon 7	MAF: 40.3%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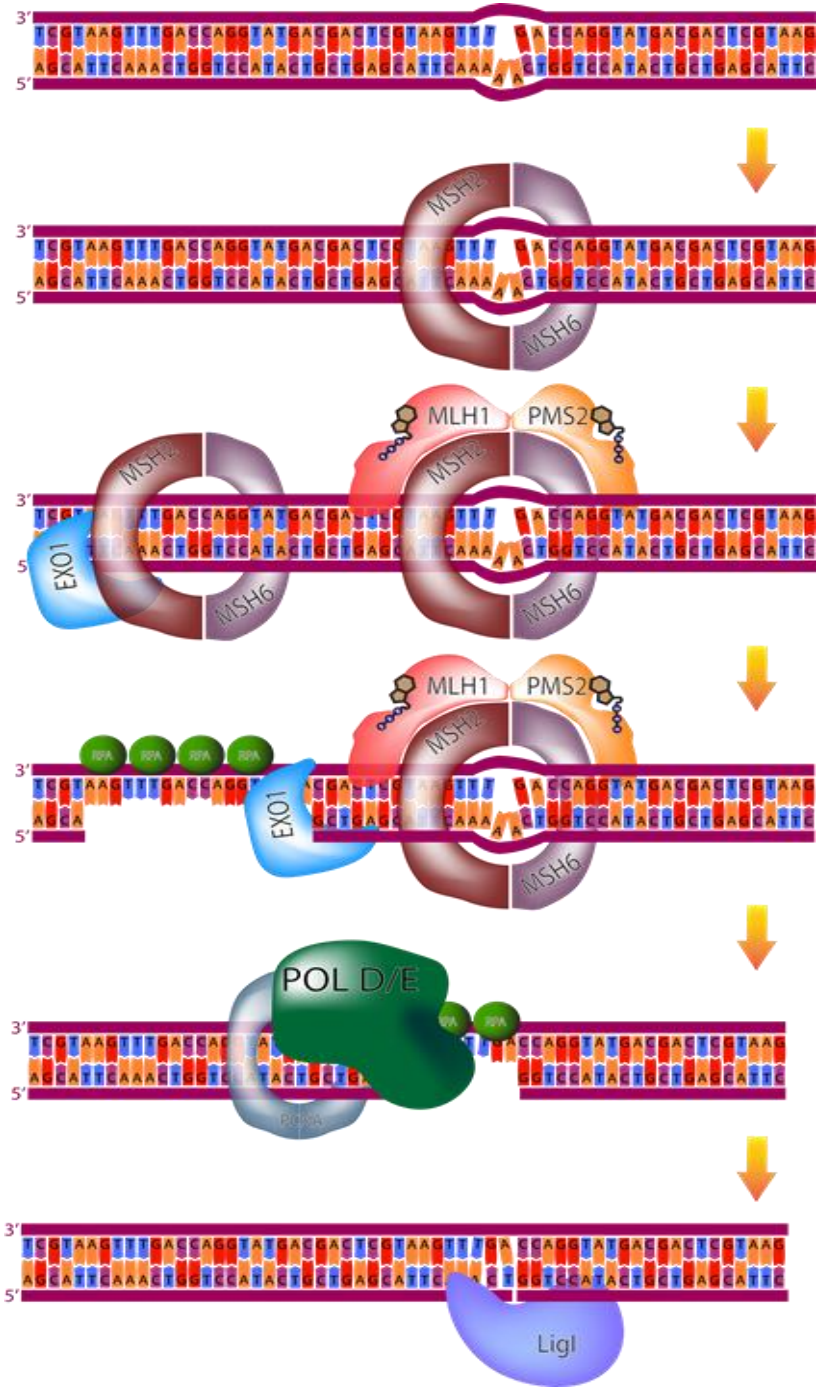
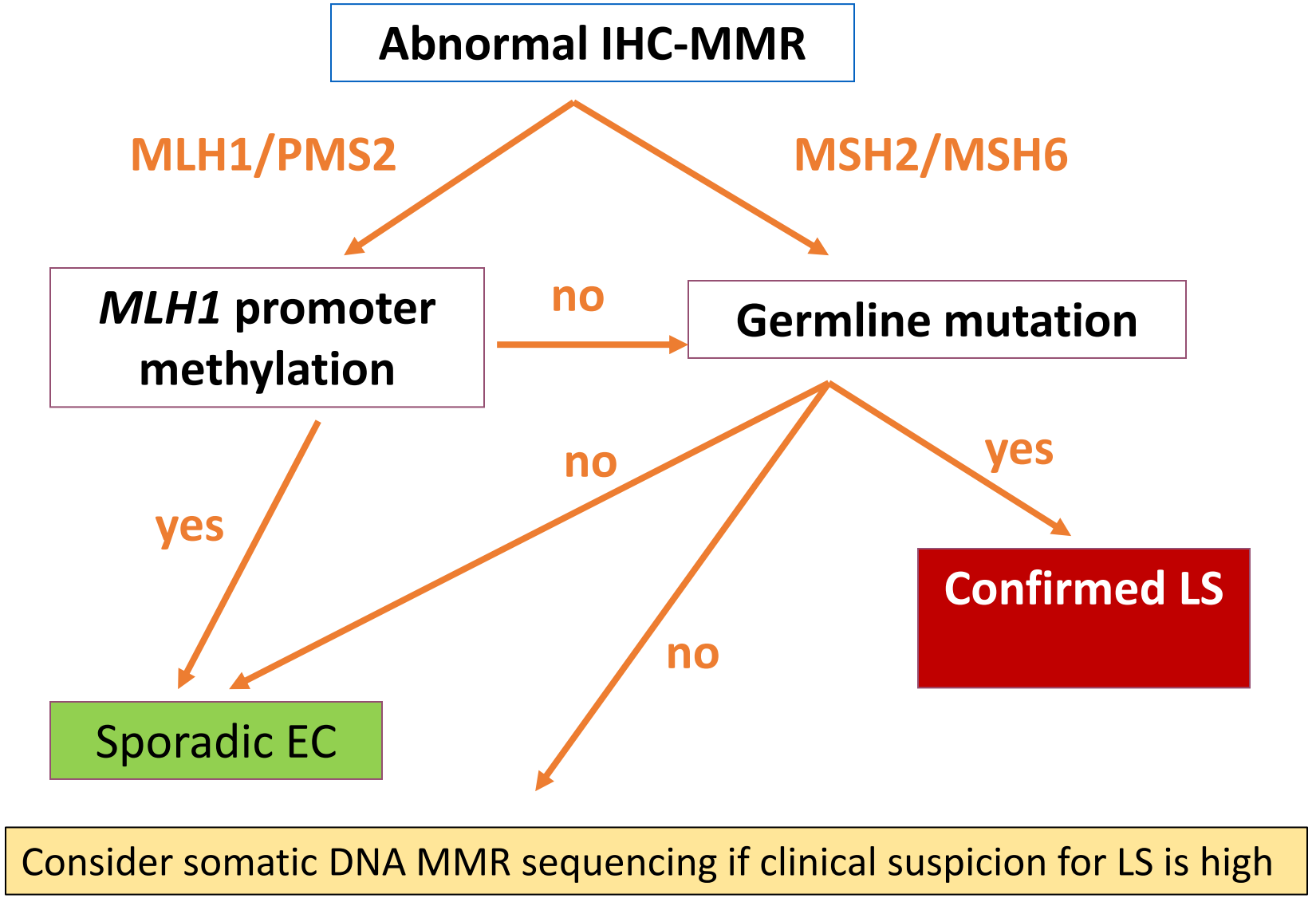
TMB
0
PTEN
PIK3CA
TP53
ARID1A
PIK3R1
KRAS
CTCF
KMT2B
ZFHX3
CTNNB1
FBXW7
PPP2R1A
BCOR
MED12
POLE
ESR1
ERBB2
CCNE1
87%
58%
18%
82%
36%
29%
47%
48%
47%
17%
17%
12%
30%
14%
17%
4%
13%
1%
Missense Mutation
Frame Shift Mutation
Nonsense Mutation
In Frame Deletion
Splice Site Alteration
Amplification
Deletion
Multiple Hits

DNA Mismatch Repair



Testing scheme



DNA mismatch repair (MMR) gene inactivation

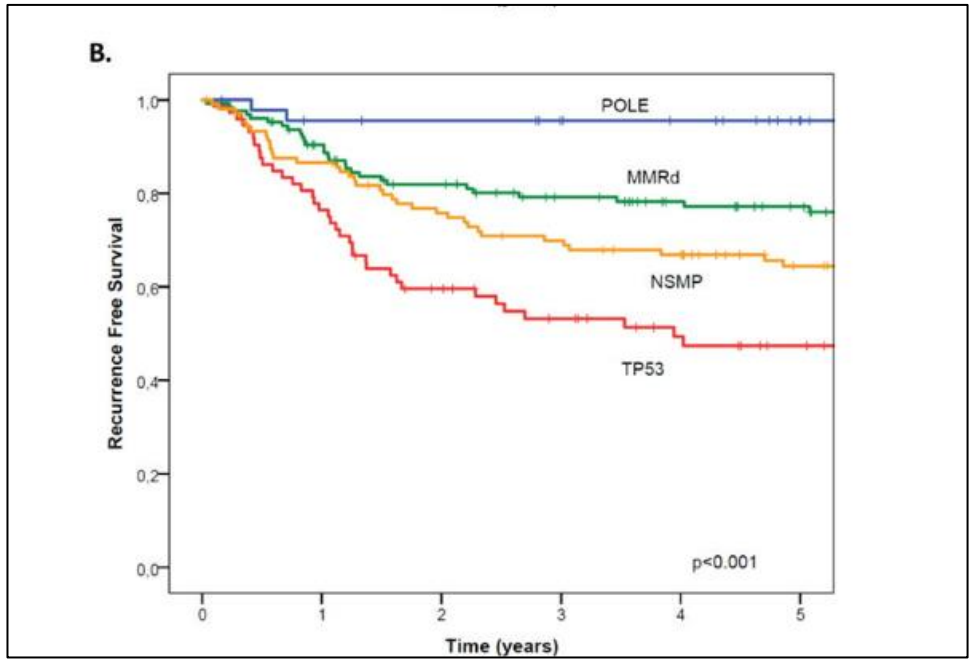
- Germline DNA MMR gene mutation
  - *MSH6, MSH2, MLH1, PMS2*
- Germline *EPCAM* mutation leading to down-regulation of MSH2 expression
- Constitutive “epimutation”

Lynch Syndrome

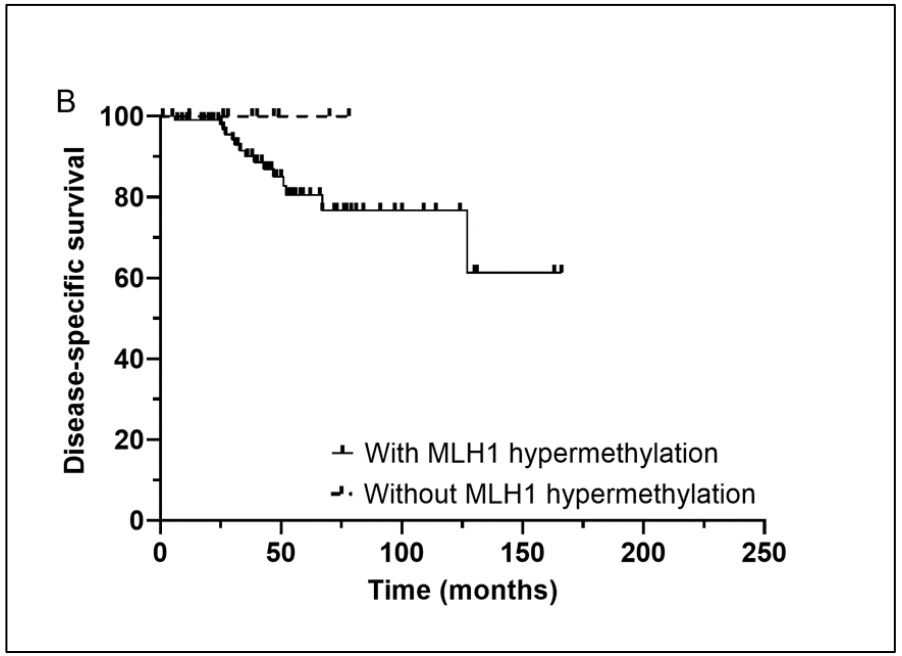
- Somatic promoter methylation (epigenetic silencing of *hMLH1*)
- Somatic gene mutation

Not Lynch Syndrome

Clinical significance of mutation vs promoter methylation

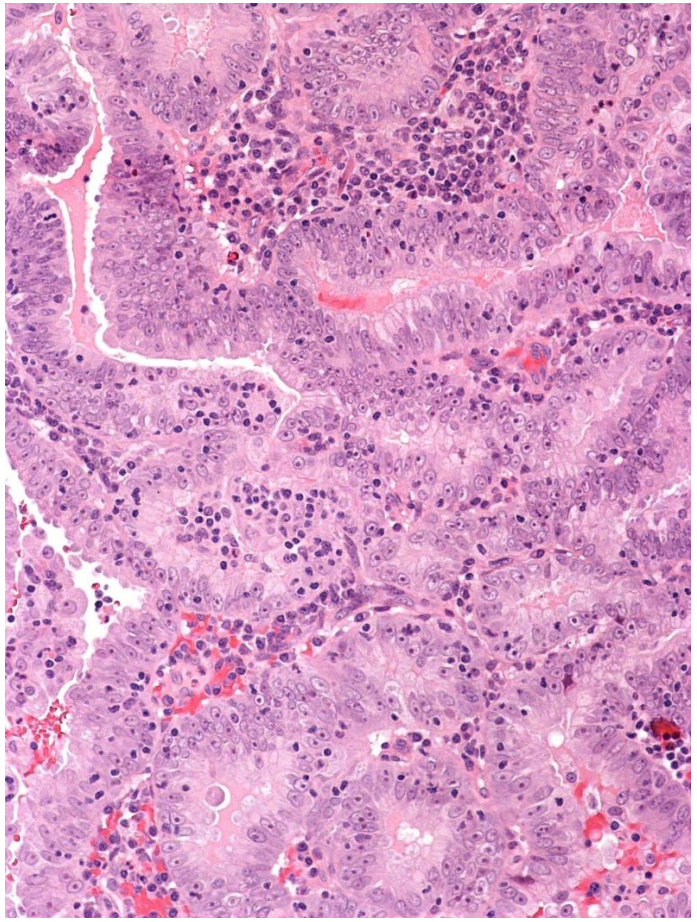


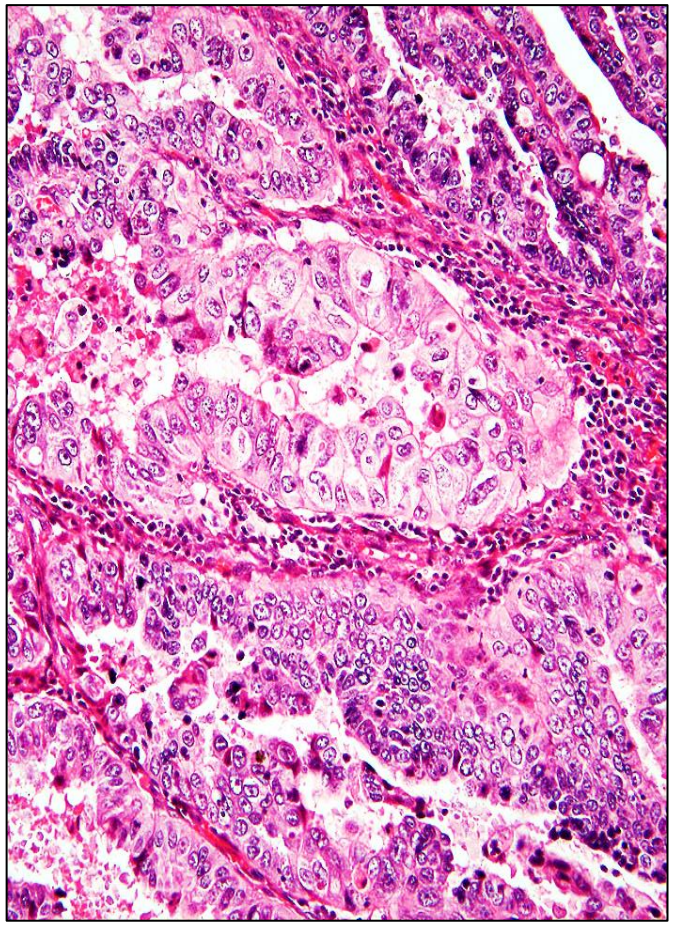
Bosse T, *et al*. *Am J Surg Pathol* 2018

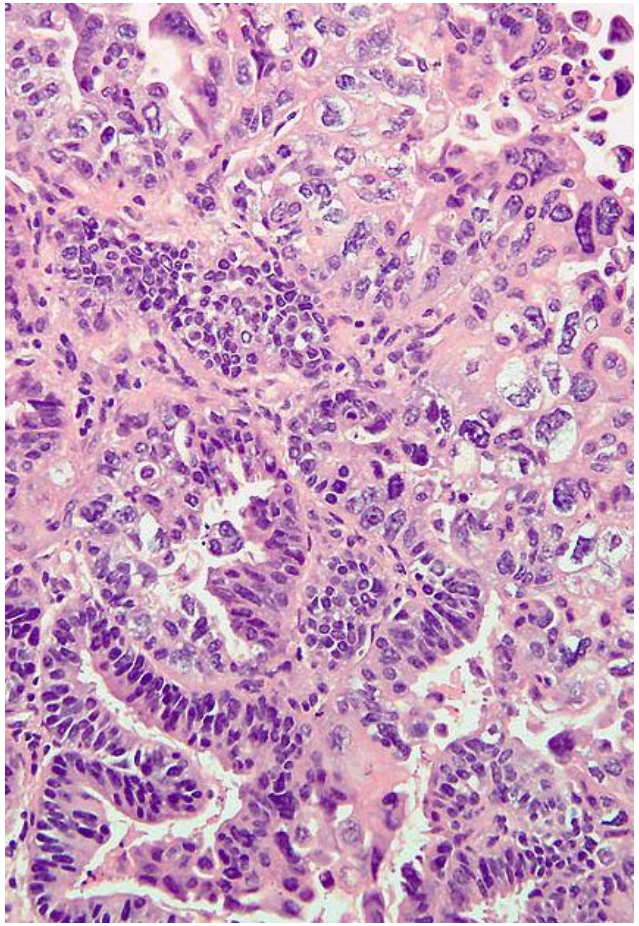


Kertwidjojo E, *et al*. *Mod Pathol* 2023

Common features of *POLE* ultramutated endometrial carcinomas







Hussein Y, Soslow R, *et al.* *Mod Pathol* 2015
Van Gool IC, *et al. Histopathology* 2018
Keyhanian K, *et al. Am J Surg Pathol* 2024

Summary	258 mutations, no copy number alterations, no structural variants detected. 5 alterations have OncoKB treatment interpretations.
MSI Status	MICROSATELLITE STABLE (MSS). See MSI note below.[β]
Tumor Mutation Burden	The estimated tumor mutation burden (TMB) for this sample is 226.5 mutations per megabase (mt/Mb). The median TMB assessed by MSK-IMPACT for all patients is 3.9 mt/Mb and for patients with Endometrial Cancer is 5.9 mt/Mb as of the date this report was issued.[γ]

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Mutations				
KIT	Missense Mutation	T632A *(c.1894A>G)*	exon 13	MAF: 26.5% 2B α
BRCA2	Nonsense Mutation	E510* *(c.1528G>T)*	exon 10	MAF: 27.6% 2B
PIK3CA	Missense Mutation	T1025A *(c.3073A>G)*	exon 21	MAF: 32.4% 3B α
PIK3CA	Missense Mutation	R38C *(c.112C>T)*	exon 2	MAF: 3.2% 3B α
PIK3CA	Missense Mutation	R88Q *(c.263G>A)*	exon 2	MAF: 24.0% 3B α
POLE	Missense Mutation	P286R *(c.857C>G)*	exon 9	MAF: 27.9%
PRKCI	Missense Mutation	R480C *(c.1438C>T)*	exon 15	MAF: 26.7%
PTEN	Missense Mutation	Y68D *(c.202T>G)*	exon 3	MAF: 23.2%
SMARCD1	Missense Mutation	R183Q *(c.548G>A)*	exon 5	MAF: 28.9%
CBL	Missense Mutation	R420Q *(c.1259G>A)*	exon 9	MAF: 29.4%
FLT3	Missense Mutation	S941L *(c.2822C>T)*	exon 23	MAF: 25.7%
PTEN	Missense Mutation	F341V *(c.1021T>G)*	exon 8	MAF: 32.6%
SMAD4	Missense Mutation	R496H *(c.1487G>A)*	exon 12	MAF: 26.5%
SPOP	Missense Mutation	E50K *(c.148G>A)*	exon 3	MAF: 26.9%
ARID1A	Nonsense Mutation	R1989* *(c.5965C>T)*	exon 20	MAF: 56.9%
ARID1A	Nonsense Mutation	S607* *(c.1820C>A)*	exon 4	MAF: 24.6%
ATM	Nonsense Mutation	R1730* *(c.5188C>T)*	exon 35	MAF: 28.6%

What makes *POLE* "POLE"?

Table 3. Pathogenic *POLE* EDM based on POLE-score

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

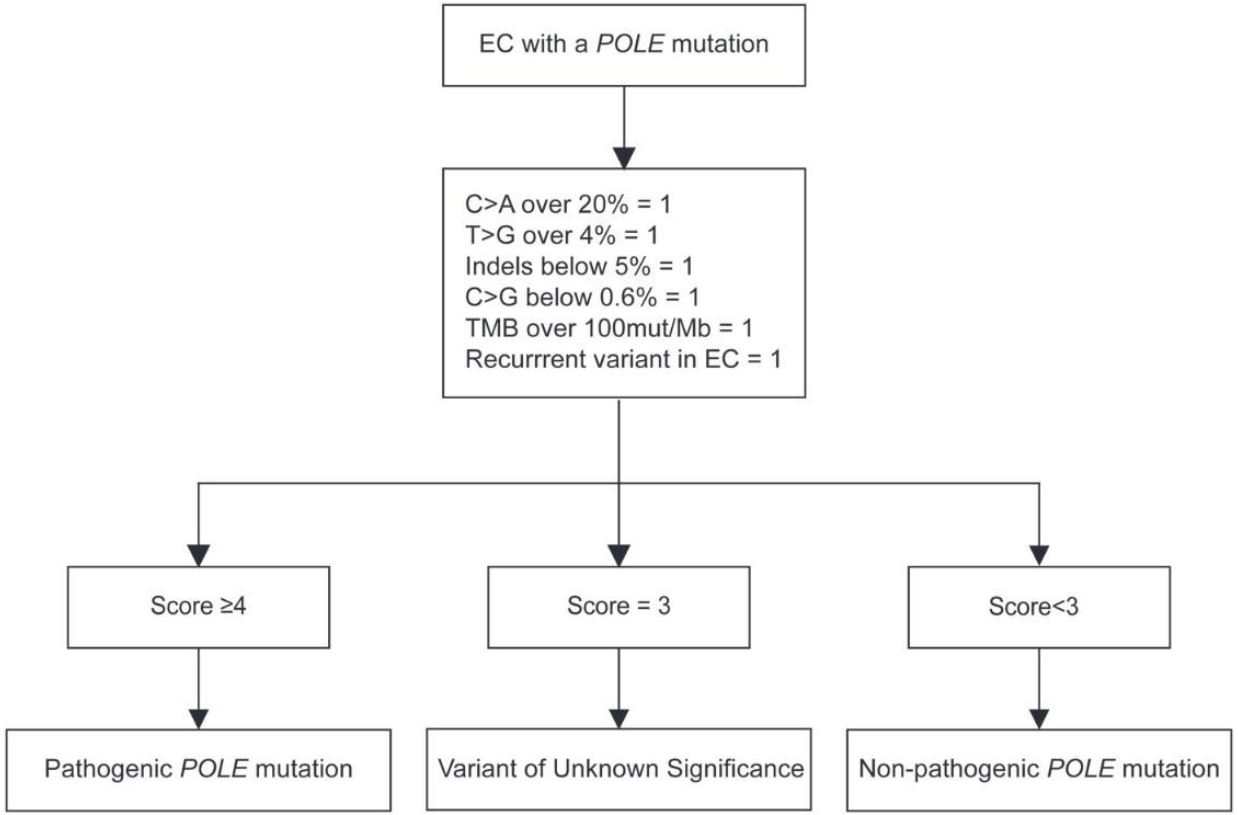
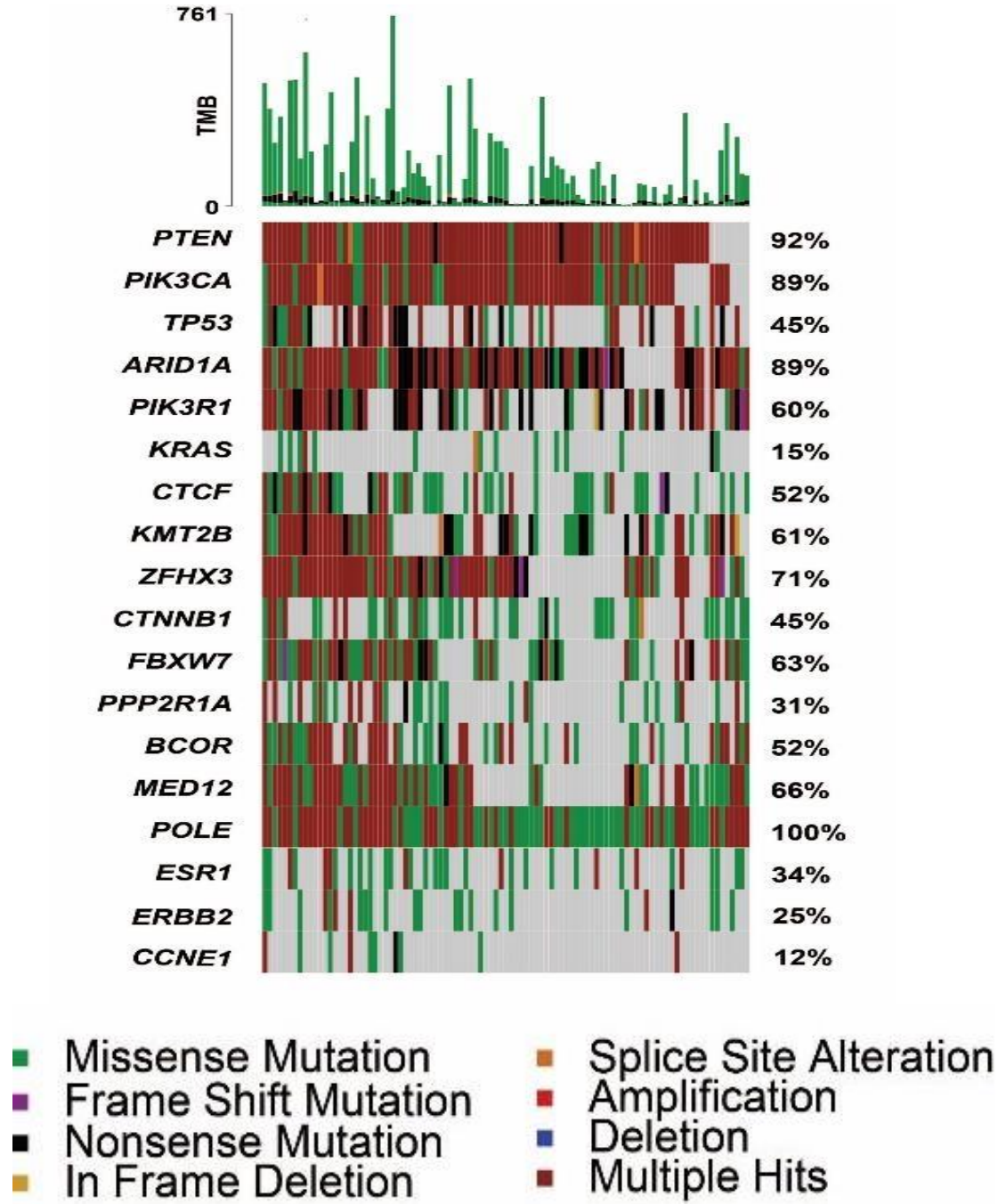


Figure 2. *POLE* genomic alteration score (POLE-score). Diagnostic scoring system based on mutation type proportion and TMB of the five hotspot *POLE* mutations, as well as the variant recurrence.

J Pathol. 2020 Mar;250(3):323-335. PMID: 31829442


761
TMB
0
PTEN 92%
PIK3CA 89%
TP53 45%
ARID1A 89%
PIK3R1 60%
KRAS 15%
CTCF 52%
KMT2B 61%
ZFHX3 71%
CTNNB1 45%
FBXW7 63%
PPP2R1A 31%
BCOR 52%
MED12 66%
POLE 100%
ESR1 34%
ERBB2 25%
CCNE1 12%
Missense Mutation
Frame Shift Mutation
Nonsense Mutation
In Frame Deletion
Splice Site Alteration
Amplification
Deletion
Multiple Hits

POLE assays

- Next generation multi-gene panel mutational testing for EDM hotspots

- QPOLE: *POLE* sequencing by multiplex genotyping qPCR

JCO Glob Oncol. 2023 May;9:e2200384.PMID: 37229628

- SNaPshot Assay for POLE exonuclease domain mutations

Int J Gynecol Pathol. 2022 Nov 1;41(6):541-551. PMID: 34907997

POLE testing may not always be necessary

- Low-grade endometrioid carcinoma
- MMR-proficient
- *p53* wild-type
- pTIa
- No lymphovascular space invasion

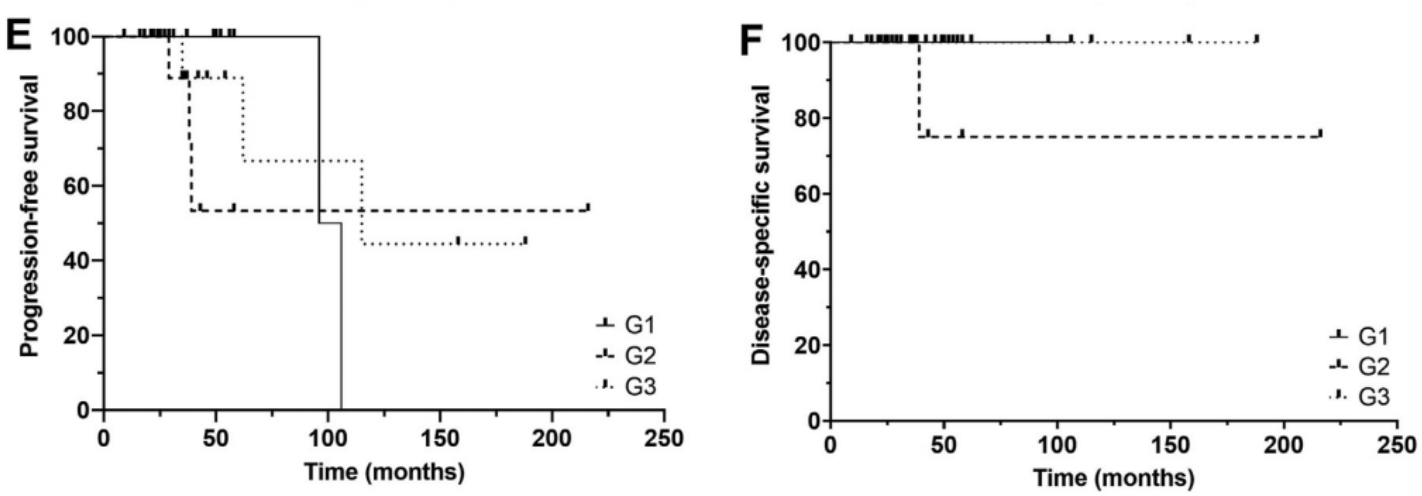
38% of hysterectomies

Int J Gynecol Pathol. 2023 Jul 1;42(4):353-363 PMID: 36731023
Mod Pathol. 2023 Apr;36(4):100085 PMID: 36788084

POLE testing strongly recommended

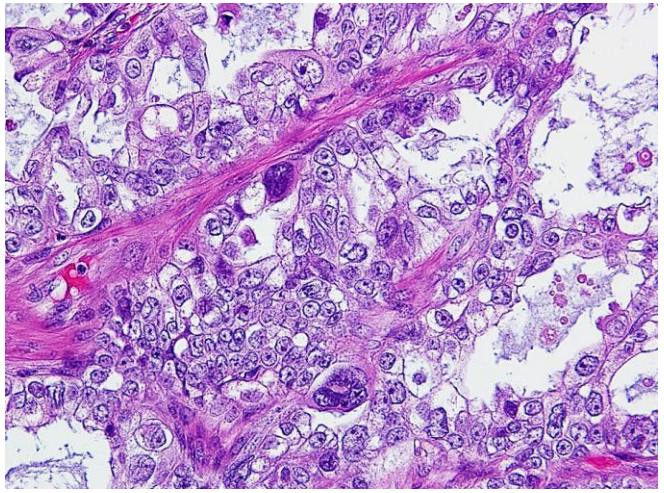
- 2023 FIGO IC and IIC, at least
  - “Aggressive histotype” limited to polyp/endometrium
  - “Aggressive histotype” with any myoinvasion

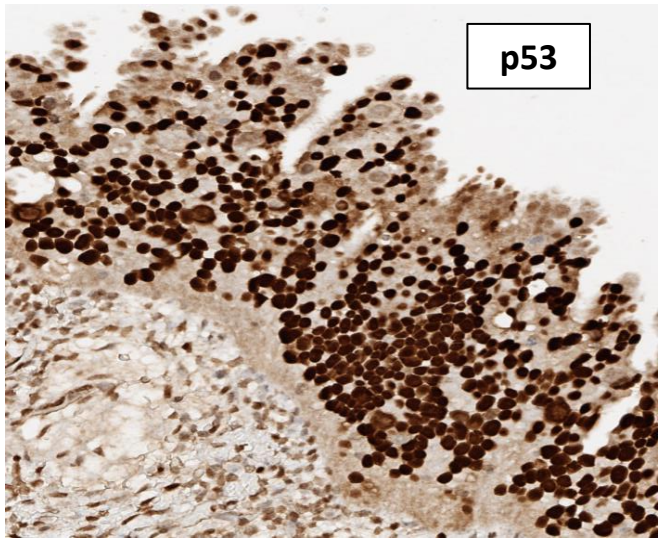
Grade and survivals in POLE

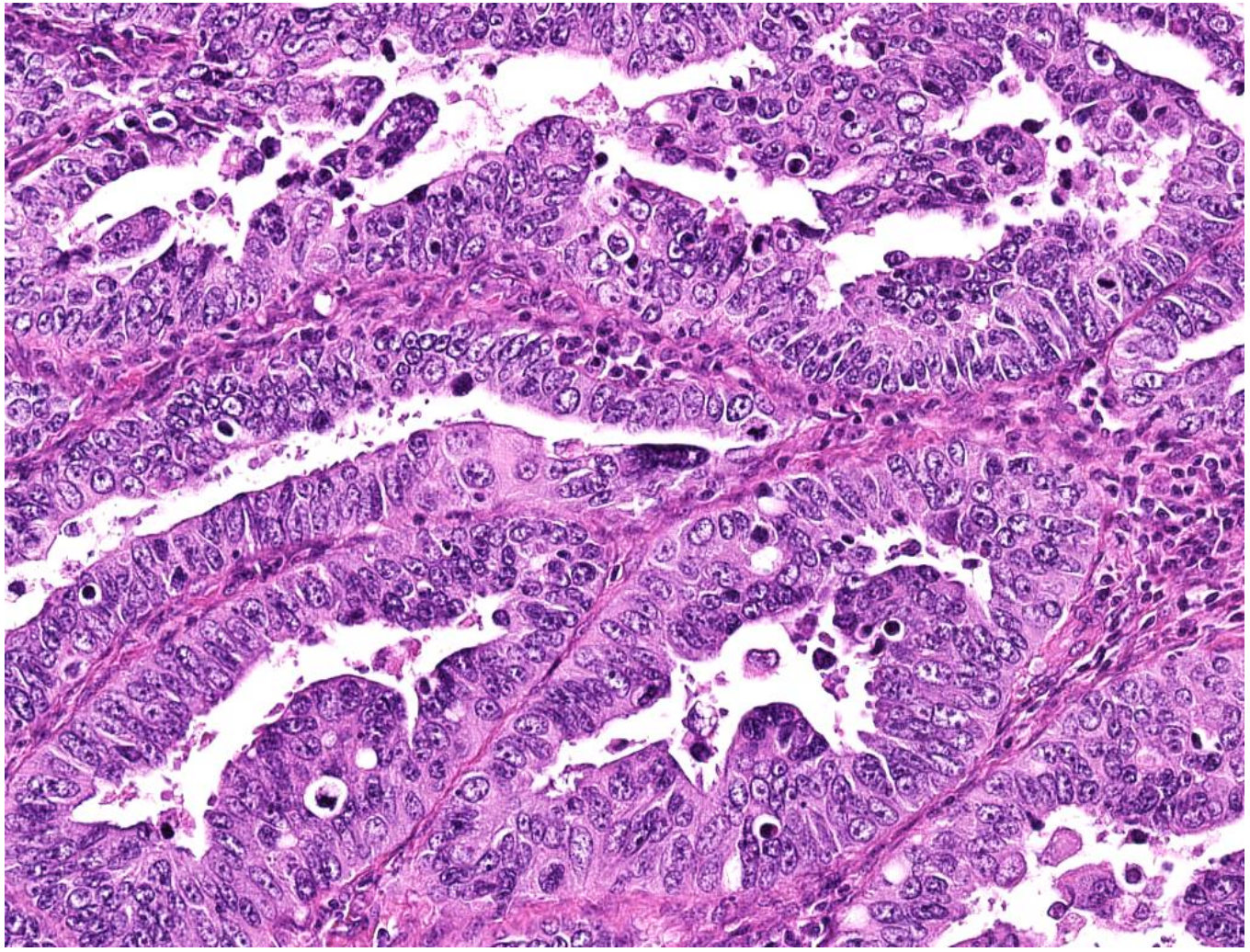


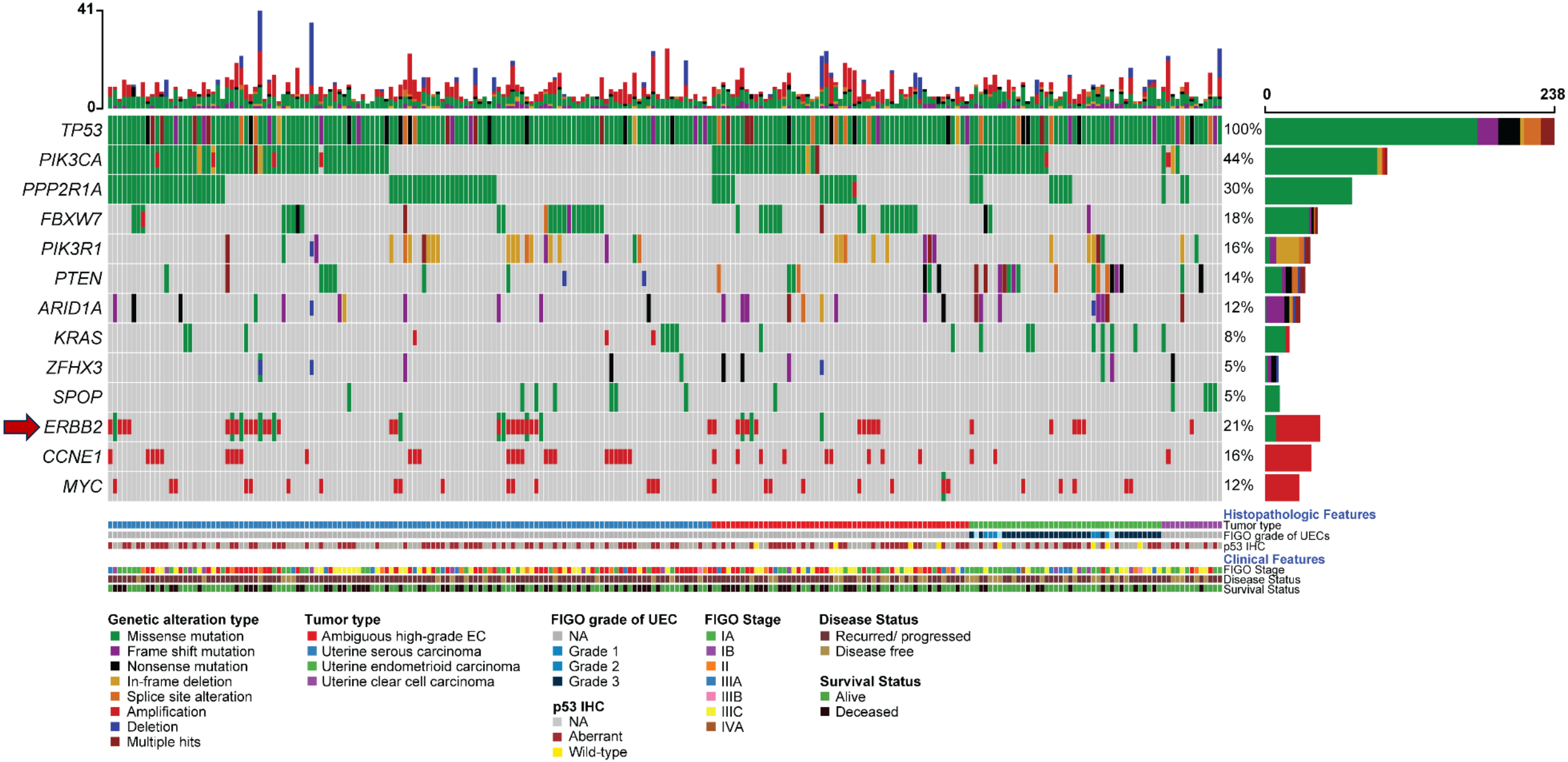
PMID: 37268062

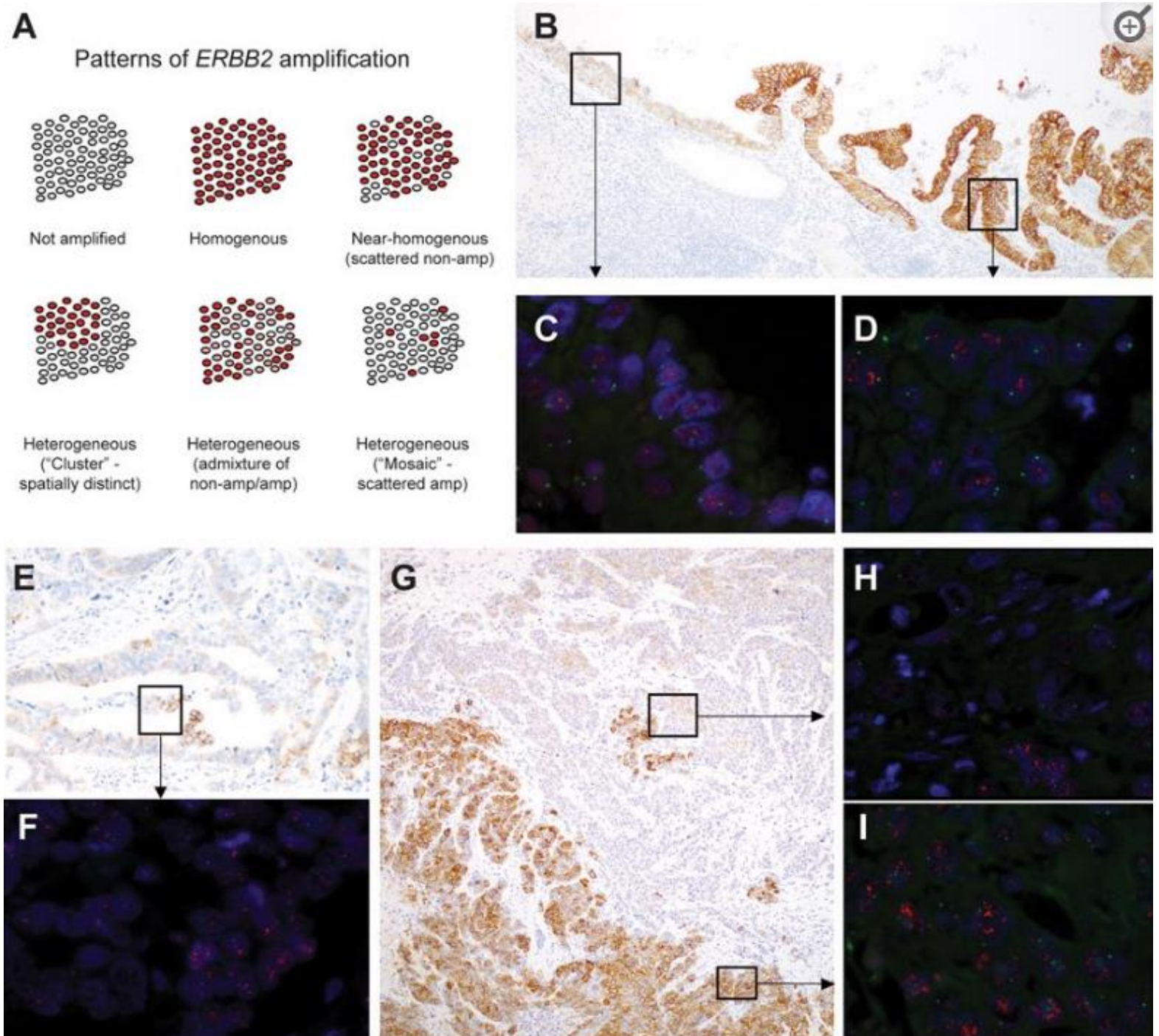
Common features of copy number high (CN-H) endometrial carcinomas








41
0
0
238
TP53
PIK3CA
PPP2R1A
FBXW7
PIK3R1
PTEN
ARID1A
KRAS
ZFHX3
SPOP
ERBB2
CCNE1
MYC
100%
44%
30%
18%
16%
14%
12%
8%
5%
5%
21%
16%
12%
Histopathologic Features
Tumor type
FIGO grade of UECs
p53 IHC
Clinical Features
FIGO Stage
Disease Status
Survival Status
Genetic alteration type
Missense mutation
Frame shift mutation
Nonsense mutation
In-frame deletion
Splice site alteration
Amplification
Deletion
Multiple hits
Tumor type
Ambiguous high-grade EC
Uterine serous carcinoma
Uterine endometrioid carcinoma
Uterine clear cell carcinoma
FIGO grade of UEC
NA
Grade 1
Grade 2
Grade 3
p53 IHC
NA
Aberrant
Wild-type
FIGO Stage
IA
IB
II
IIIA
IIIB
IIIC
IVA
Disease Status
Recurred/ progressed
Disease free
Survival Status
Alive
Deceased



Ross DS, *et al. Mod Pathol* 2022

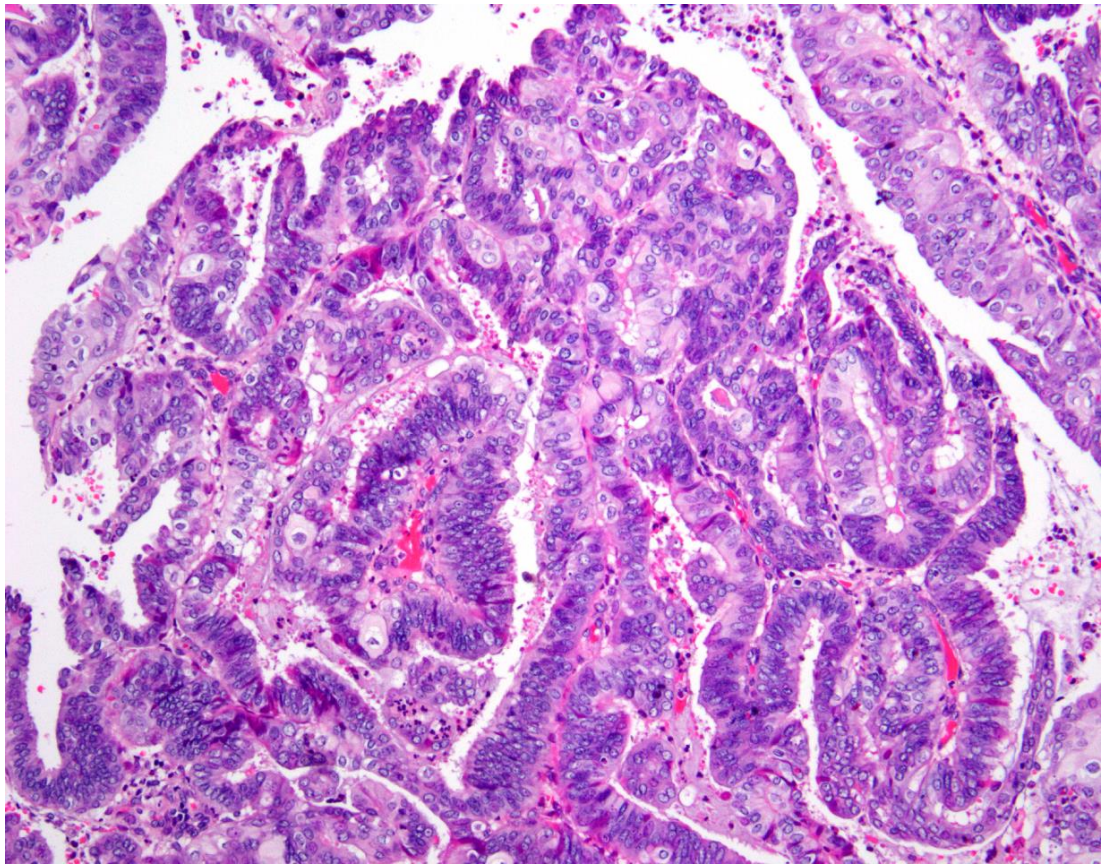
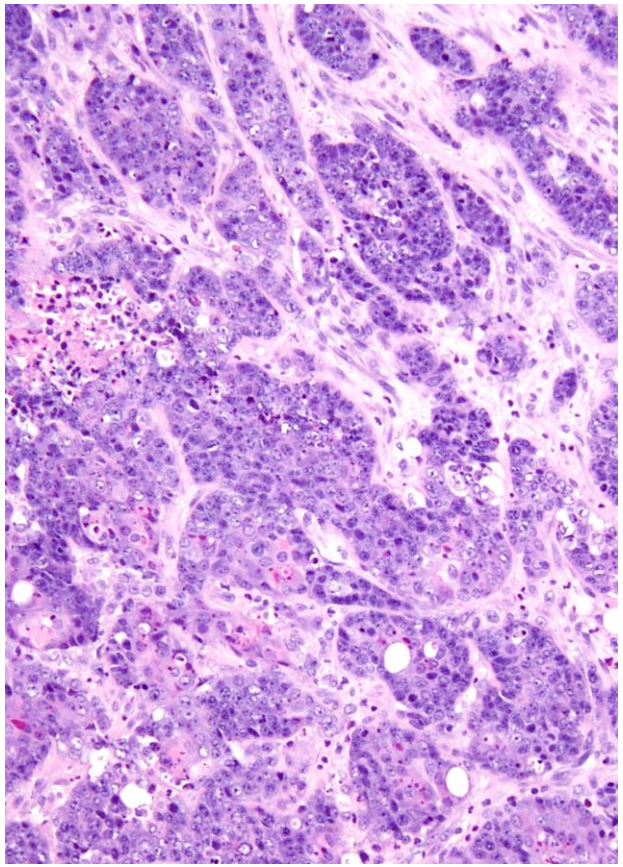
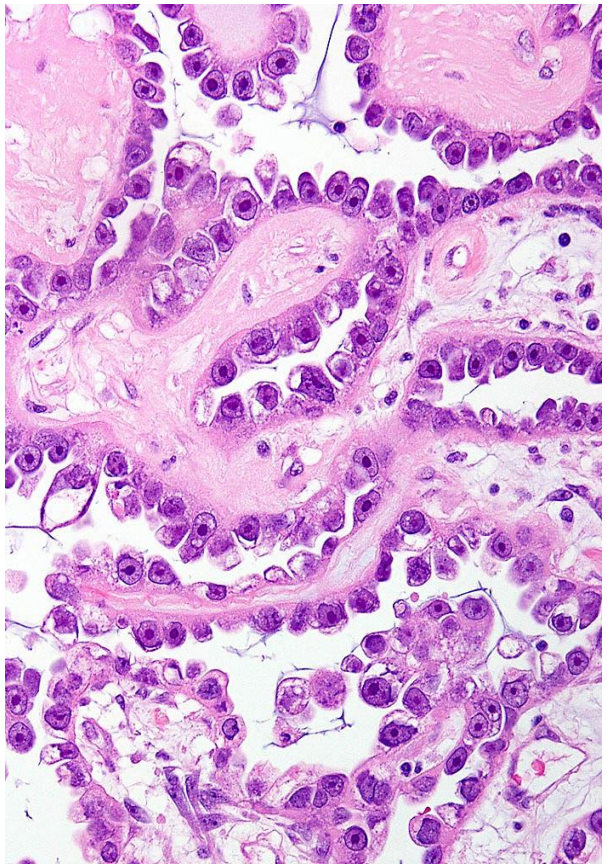
CN-H: Are they all equally bad?

- CN-H serous ~ endometrioid ~ clear cell

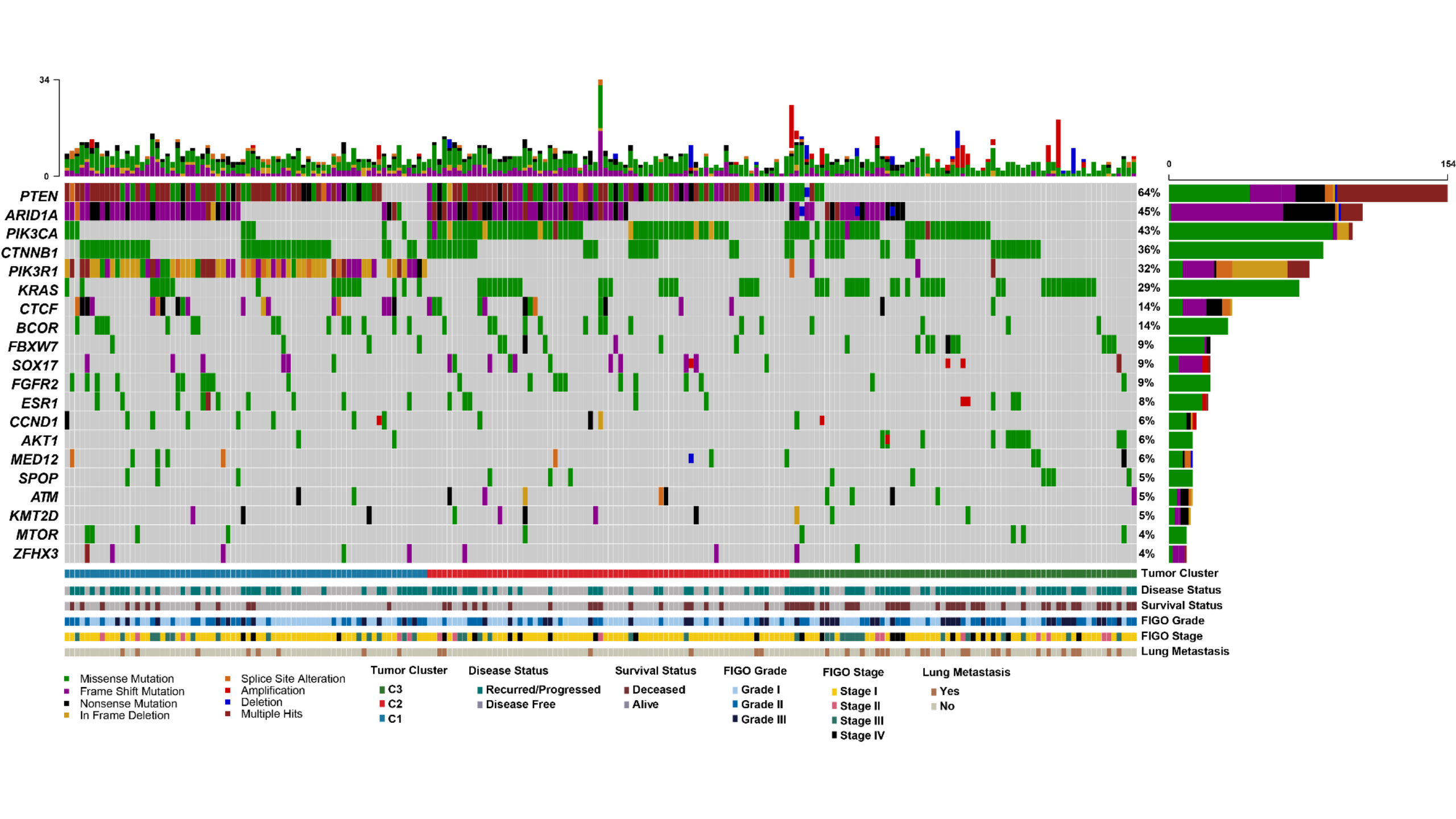
BUT

- CN-H carcinosarcoma
- CN-H carcinomas with divergent differentiation
  - Yolk sac-like
  - Choriocarcinoma
  - Trophoblastic

Features of copy number low (CN-L/NSMP) endometrial carcinomas

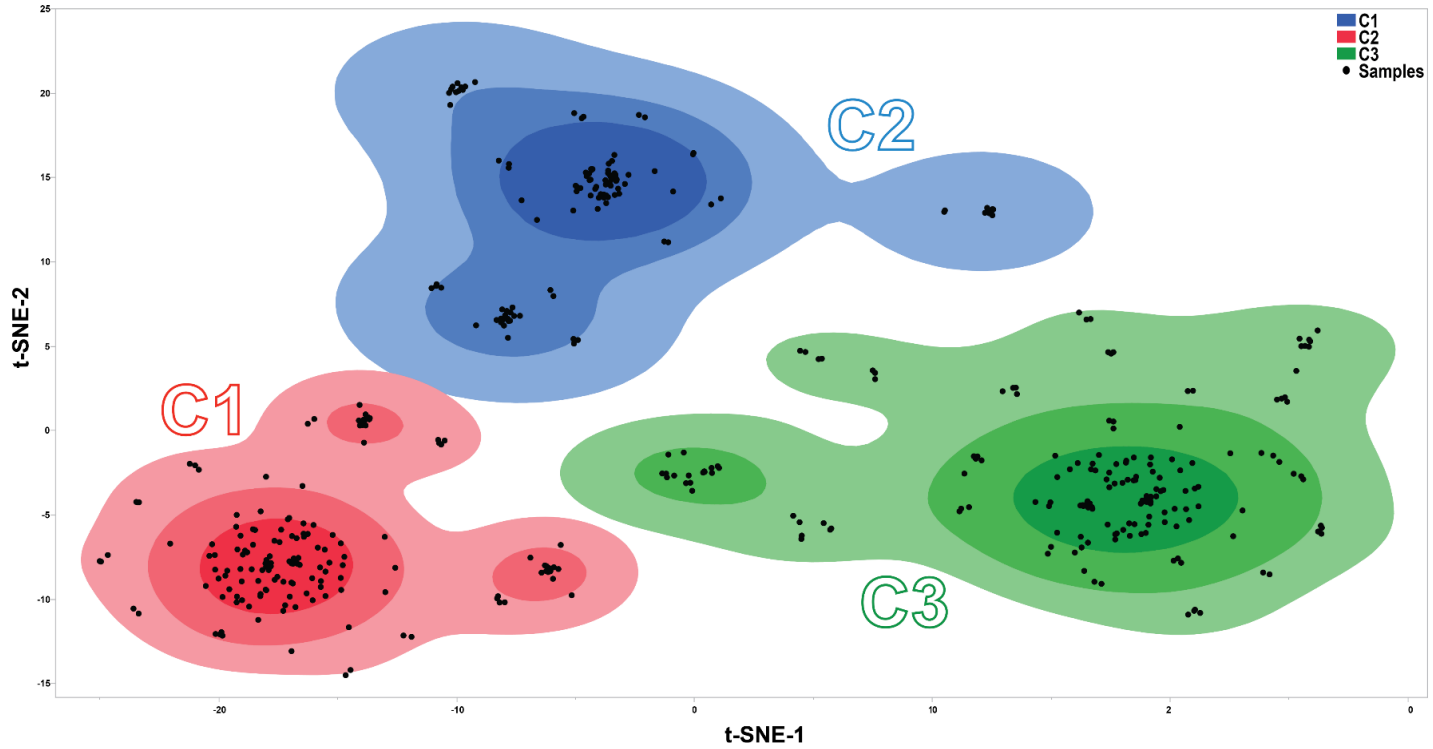




*The only molecular group in which **grade** and **histotype** are clinically important*


34
0
0
154
PTEN
ARID1A
PIK3CA
CTNNB1
PIK3R1
KRAS
CTCF
BCOR
FBXW7
SOX17
FGFR2
ESR1
CCND1
AKT1
MED12
SPOP
ATM
KMT2D
MTOR
ZFHX3
64%
45%
43%
36%
32%
29%
14%
14%
9%
9%
9%
8%
6%
6%
6%
5%
5%
5%
4%
4%
Tumor Cluster
Disease Status
Survival Status
FIGO Grade
FIGO Stage
Lung Metastasis
Missense Mutation
Frame Shift Mutation
Nonsense Mutation
In Frame Deletion
Splice Site Alteration
Amplification
Deletion
Multiple Hits
Tumor Cluster
C3
C2
C1
Disease Status
Recurred/Progressed
Disease Free
Survival Status
Deceased
Alive
FIGO Grade
Grade I
Grade II
Grade III
FIGO Stage
Stage I
Stage II
Stage III
Stage IV
Lung Metastasis
Yes
No

Aggressive CN-L subsets

- ER negative
- 1q gains
- *PTEN* wt
- Non-endometrioid
- Histologically high grade

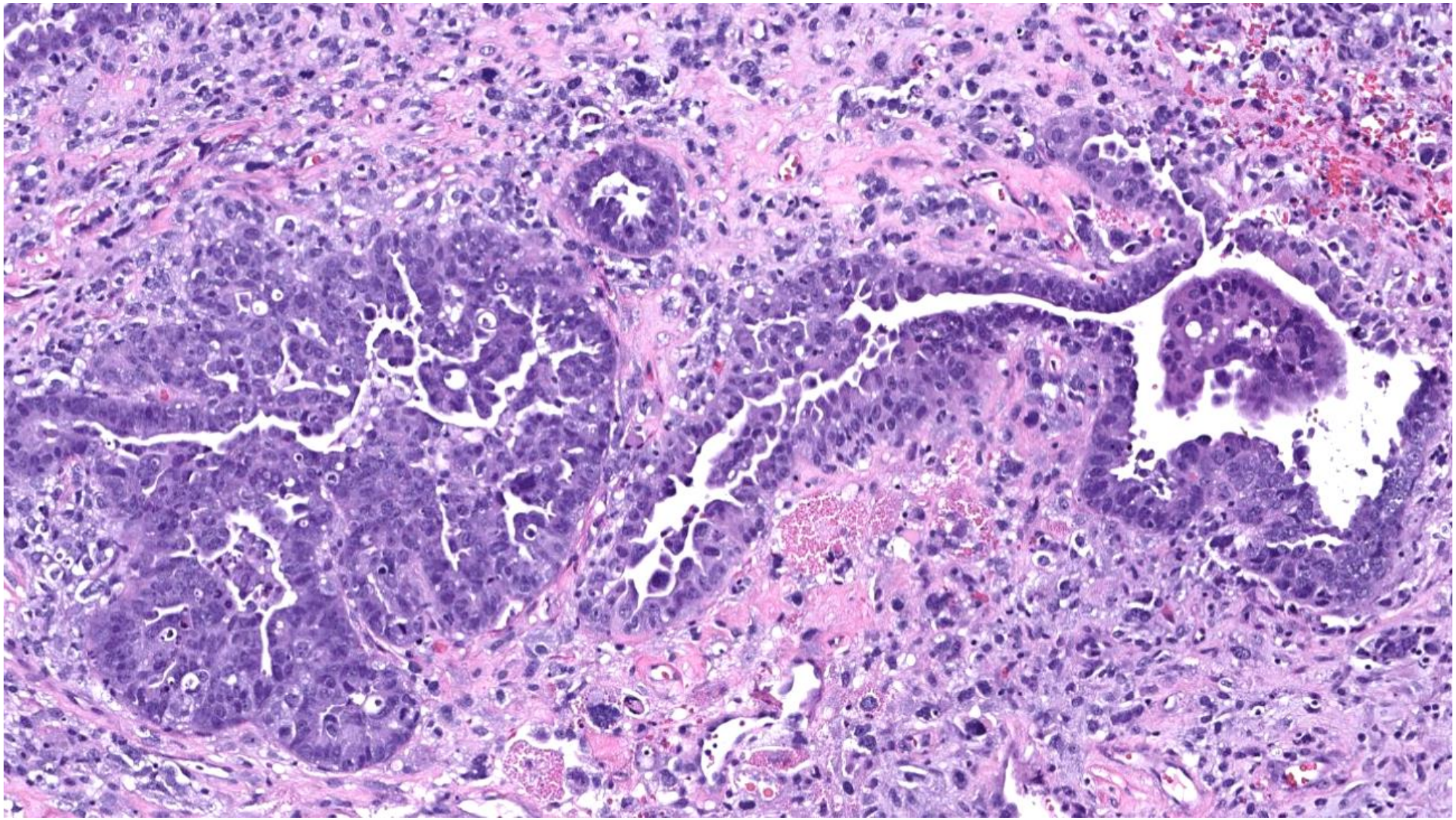


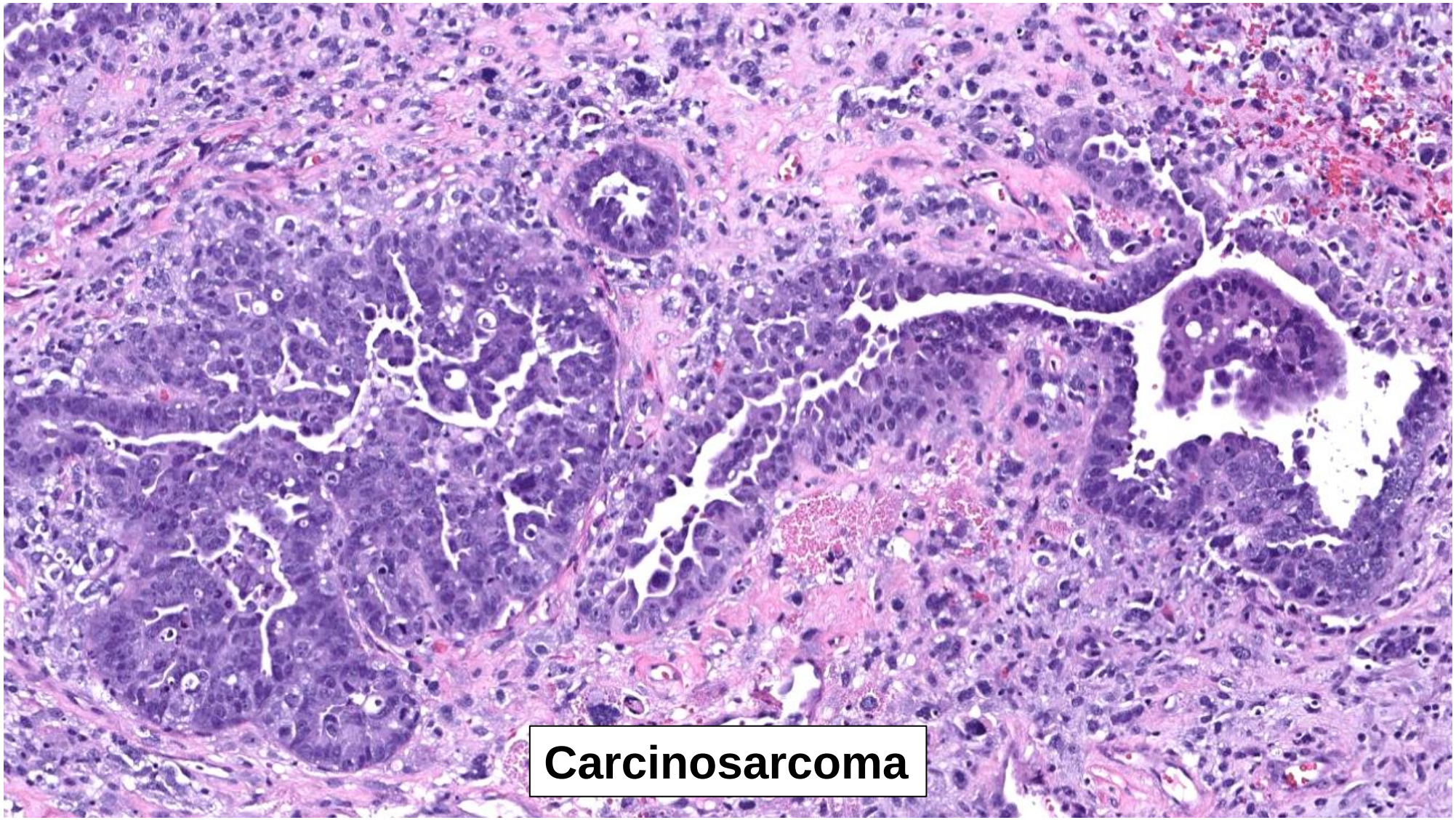
Mod Pathol 2022 Sep;35(9):1269-1278

Some more interesting endometrial carcinomas

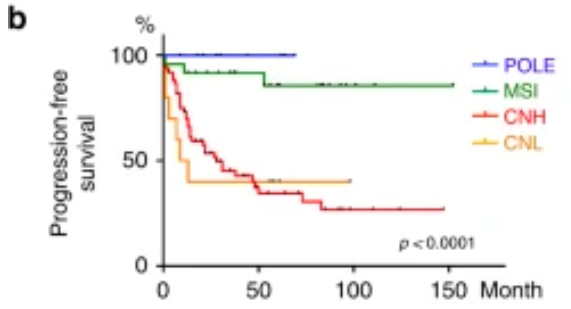
Case presentation

- 70 year-old patient
- FIGO stage IIC (2023)

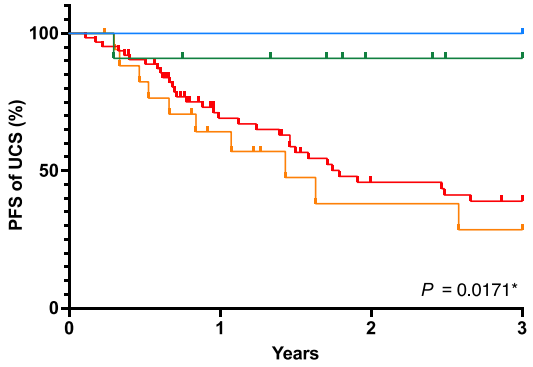



Carcinosarcoma

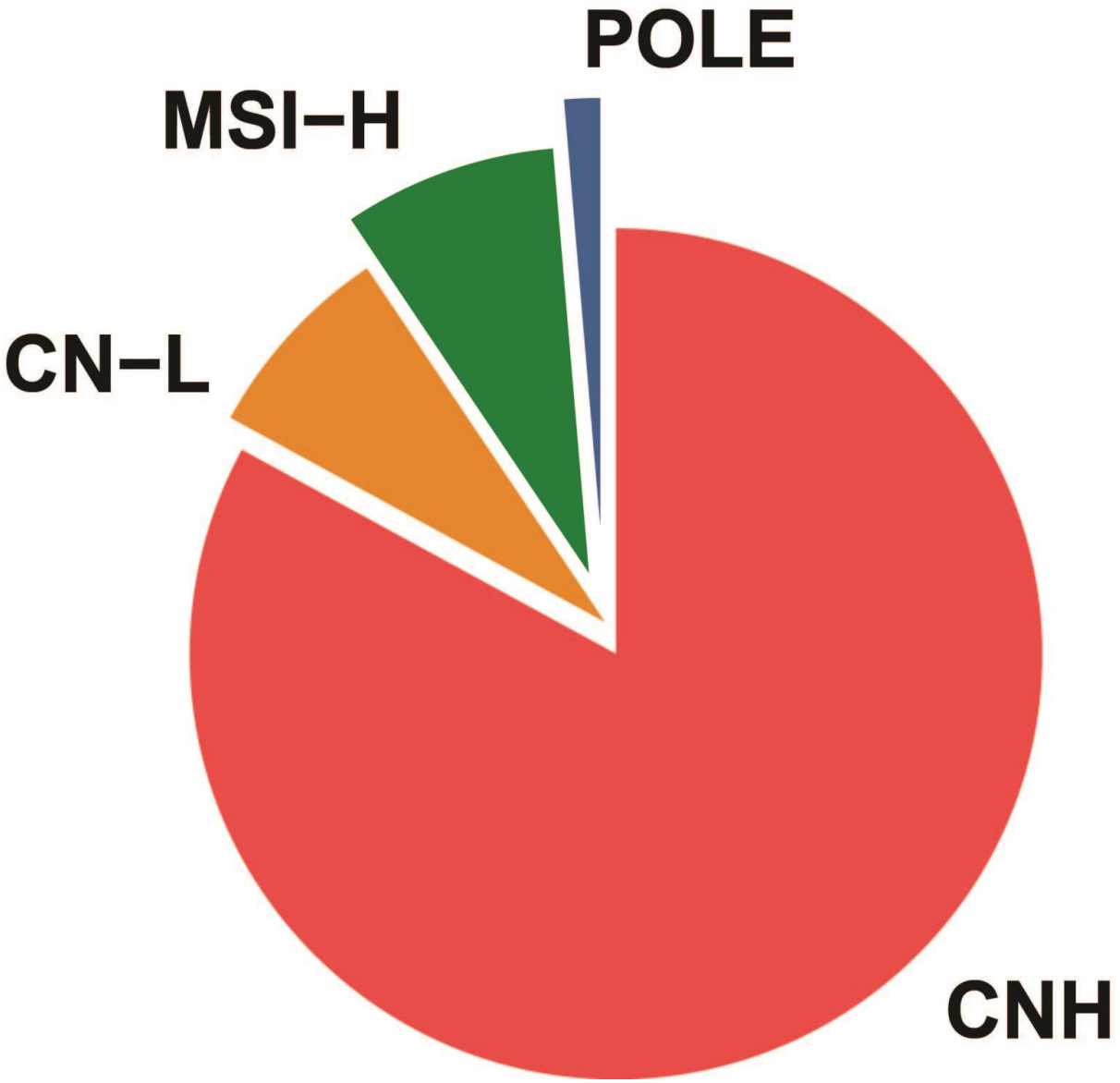
Carcinosarcoma



Gotoh, O., *et al. Nat Commun* 2019



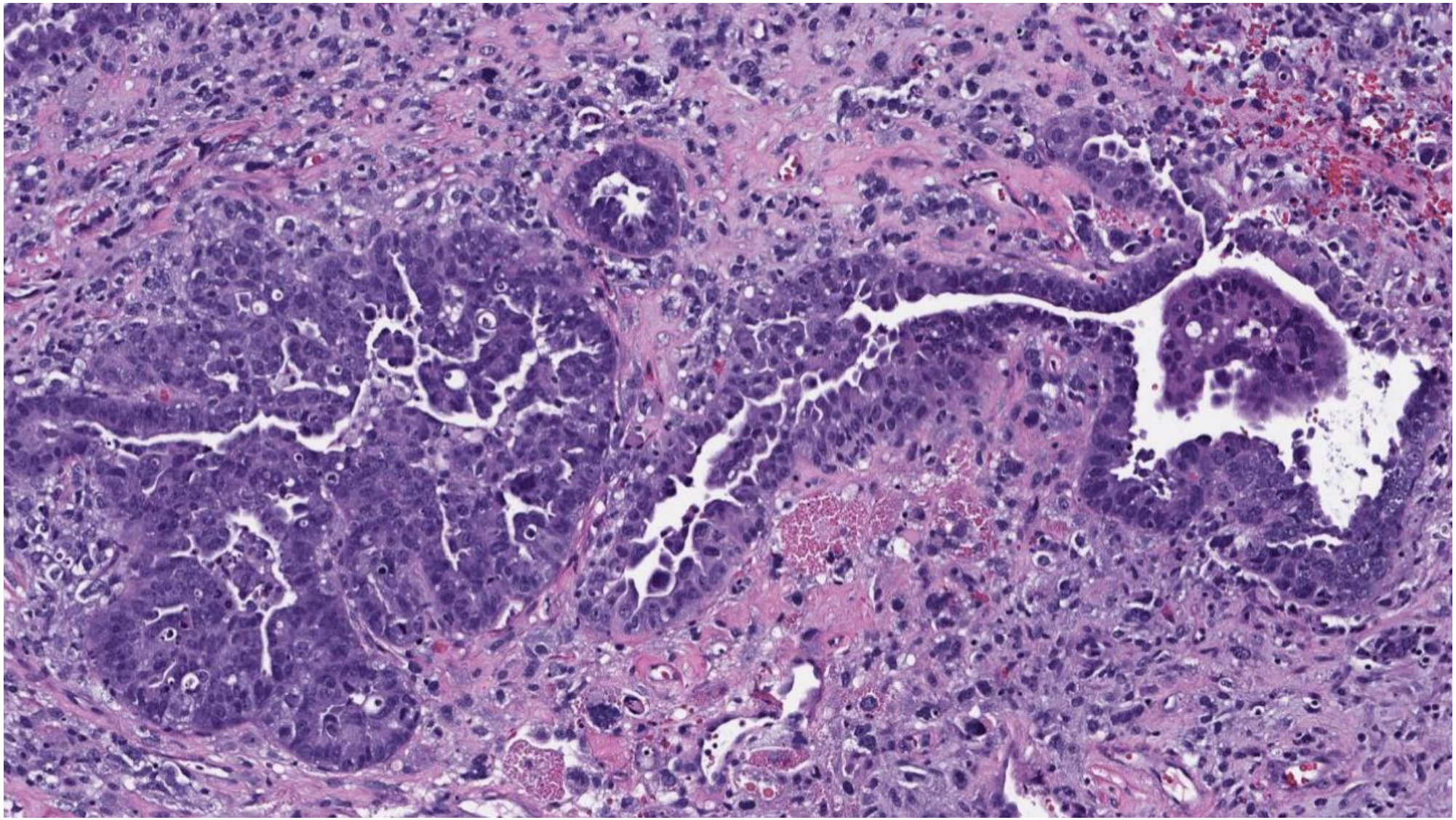
Howitt BE and Hammer PM, unpublished data



Summary	494 mutations, no copy number alterations, no structural variants detected. 3 alterations have OncoKB treatment interpretations.
MSI Status	MICROSATELLITE STABLE (MSS). See MSI note below.[β]
Tumor Mutation Burden	The estimated tumor mutation burden (TMB) for this sample is 407.0 mutations per megabase (mt/Mb). The median TMB assessed by MSK-IMPACT for all patients is 3.9 mt/Mb and for patients with Endometrial Cancer is 6.1 mt/Mb as of the date this report was issued.[γ] 1
Comments	A POLE/ POLD1 ultramutator phenotype (an abundance of alterations with a strand bias for C>A mutations at TpCpT context and T>G mutations at TpTpT context) is seen, likely as a result of POLE p.V411L.

Somatic alterations detected in this sample:

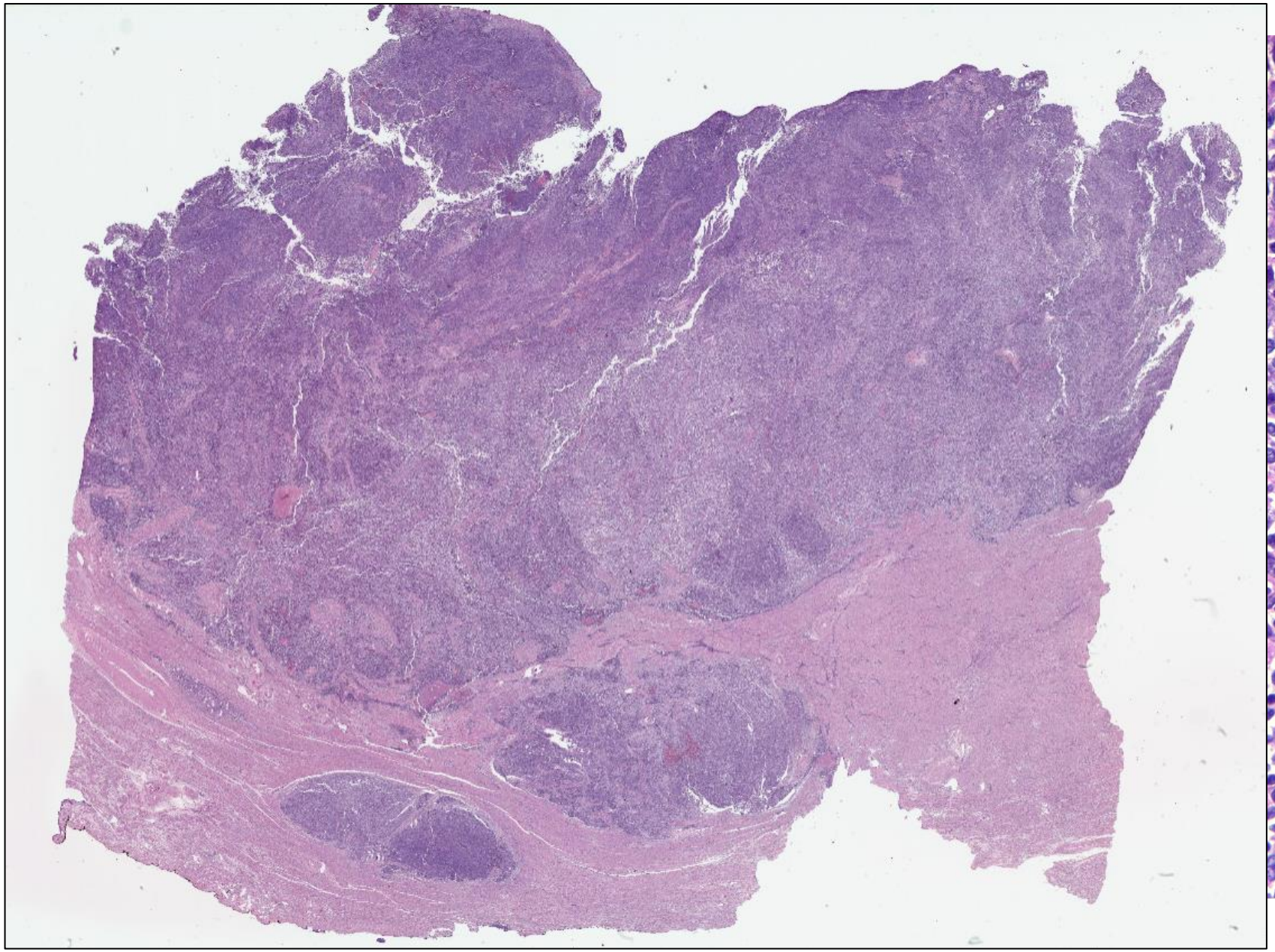
Gene	Type	Alteration	Location	Additional Information
Mutations				
PIK3CA	Missense Mutation	D939G *(c.2816A>G)*	exon 20	MAF: 22.7% 3B
ERCC2	Missense Mutation	R631H *(c.1892G>A)*	exon 20	MAF: 24.0% 3B
BRCA1	Nonsense Mutation	E1214* *(c.3640G>T)*	exon 10	MAF: 25.1% 3B d
KRAS	Missense Mutation	G13D *(c.38G>A)*	exon 2	MAF: 5.1% 4
PTEN	Missense Mutation	R173H *(c.518G>A)*	exon 6	MAF: 22.0% 4
PTEN	Missense Mutation	D252G *(c.755T>G)*	exon 7	MAF: 24.5% 4
ARID1A	Nonsense Mutation	Q1579* *(c.4735C>T)*	exon 18	MAF: 24.3% 4
PTEN	Nonsense Mutation	R335* *(c.1003C>T)*	exon 8	MAF: 27.1% 4
CASP8	Missense Mutation	R292Q *(c.875G>A)*	exon 7	MAF: 23.1%
CDH1	Missense Mutation	D254N *(c.760G>A)*	exon 6	MAF: 23.6%
POLE	Missense Mutation	V411L *(c.1231G>C)*	exon 13	MAF: 26.9%
PRKCI	Missense Mutation	R480C *(c.1438C>T)*	exon 15	MAF: 18.5%
RAF1	Missense Mutation	S257L *(c.770C>T)*	exon 7	MAF: 5.1%
TP53	Missense Mutation	R181C *(c.541C>T)*	exon 5	MAF: 21.9%

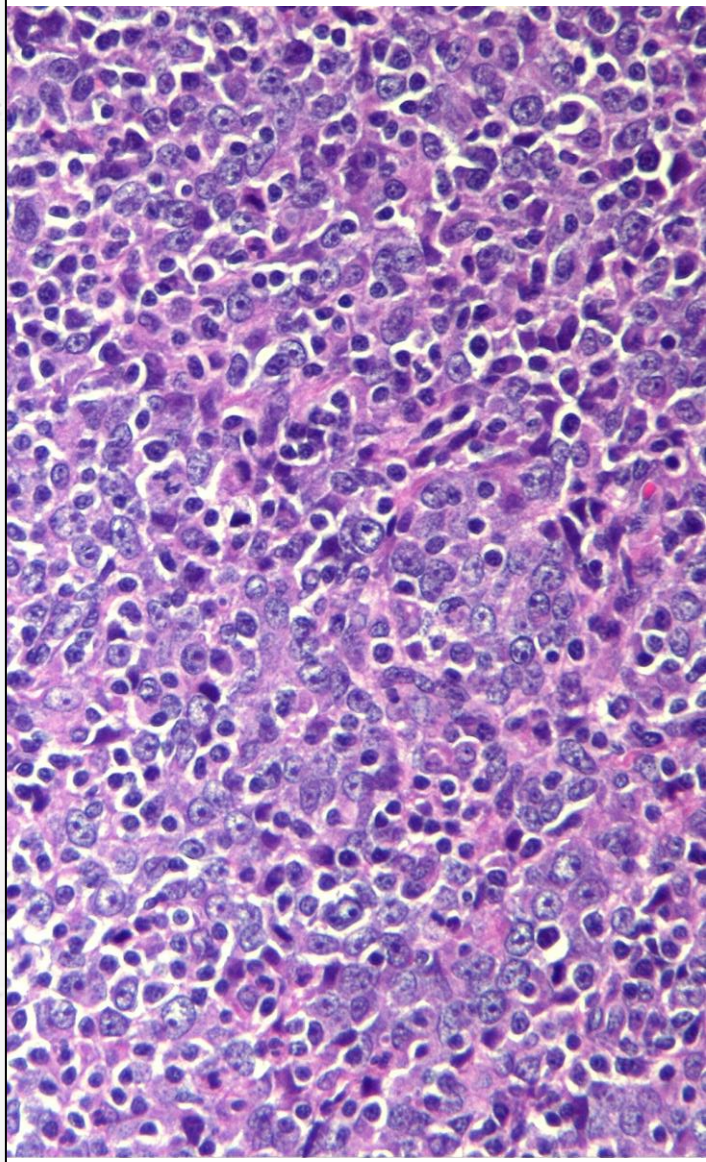


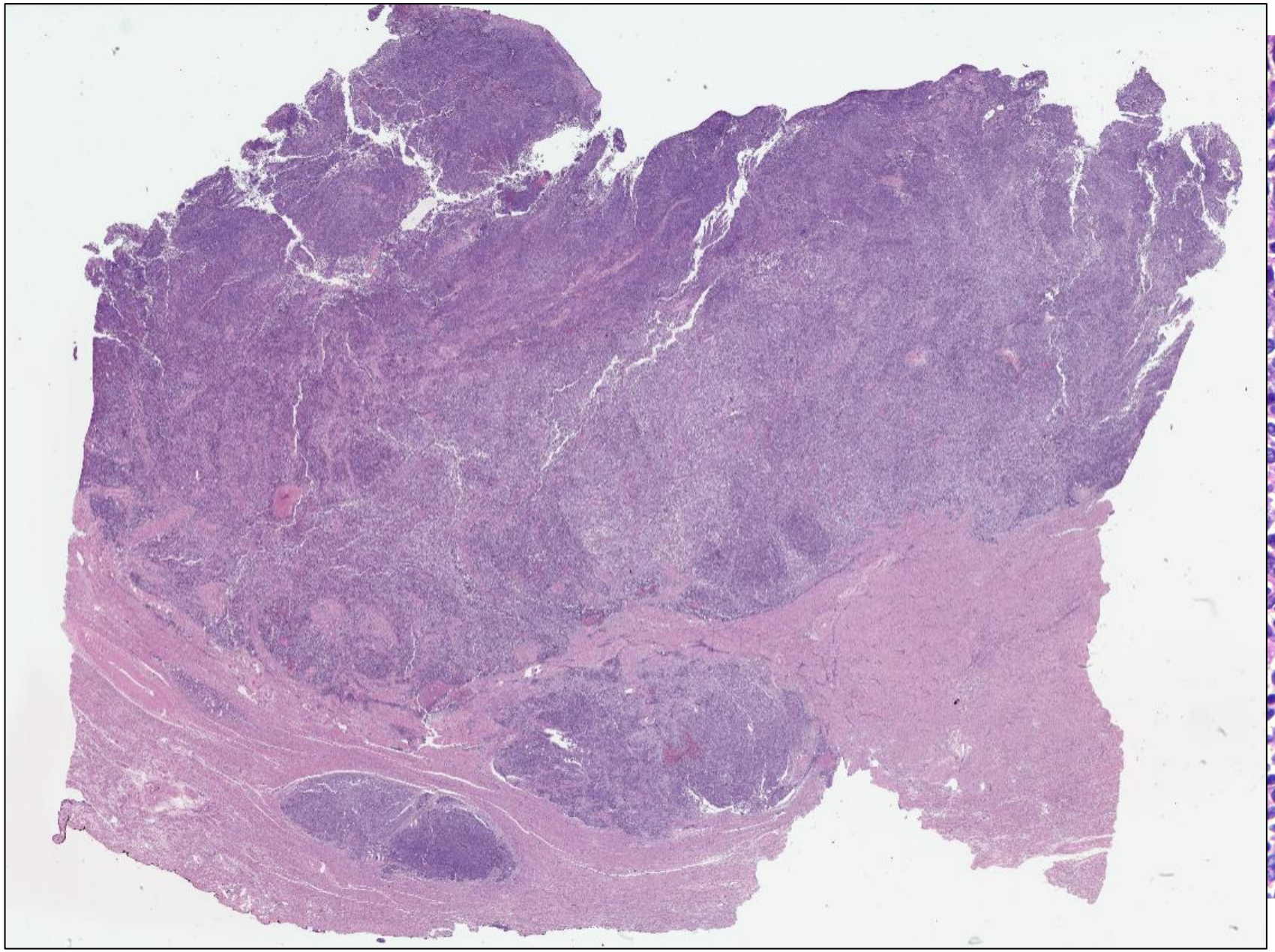
***POLE* carcinosarcoma**

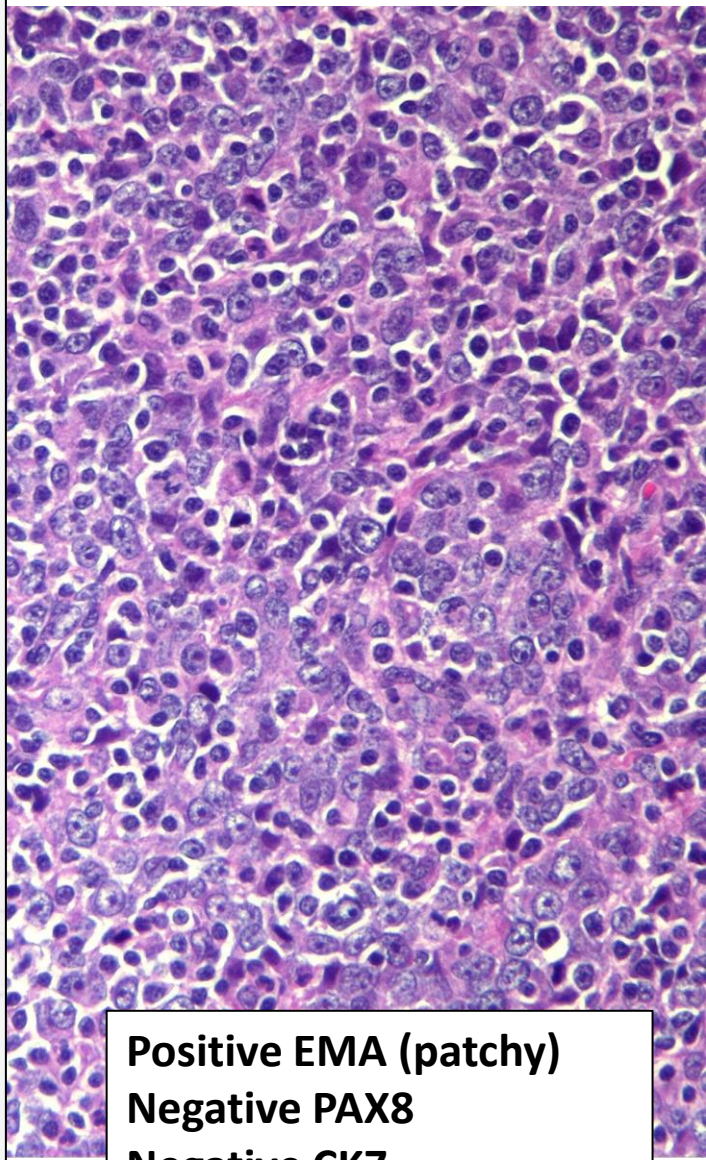
Case presentation

- 55 year-old patient
- FIGO stage IIIC2 (2023) with para-aortic lymph node metastasis

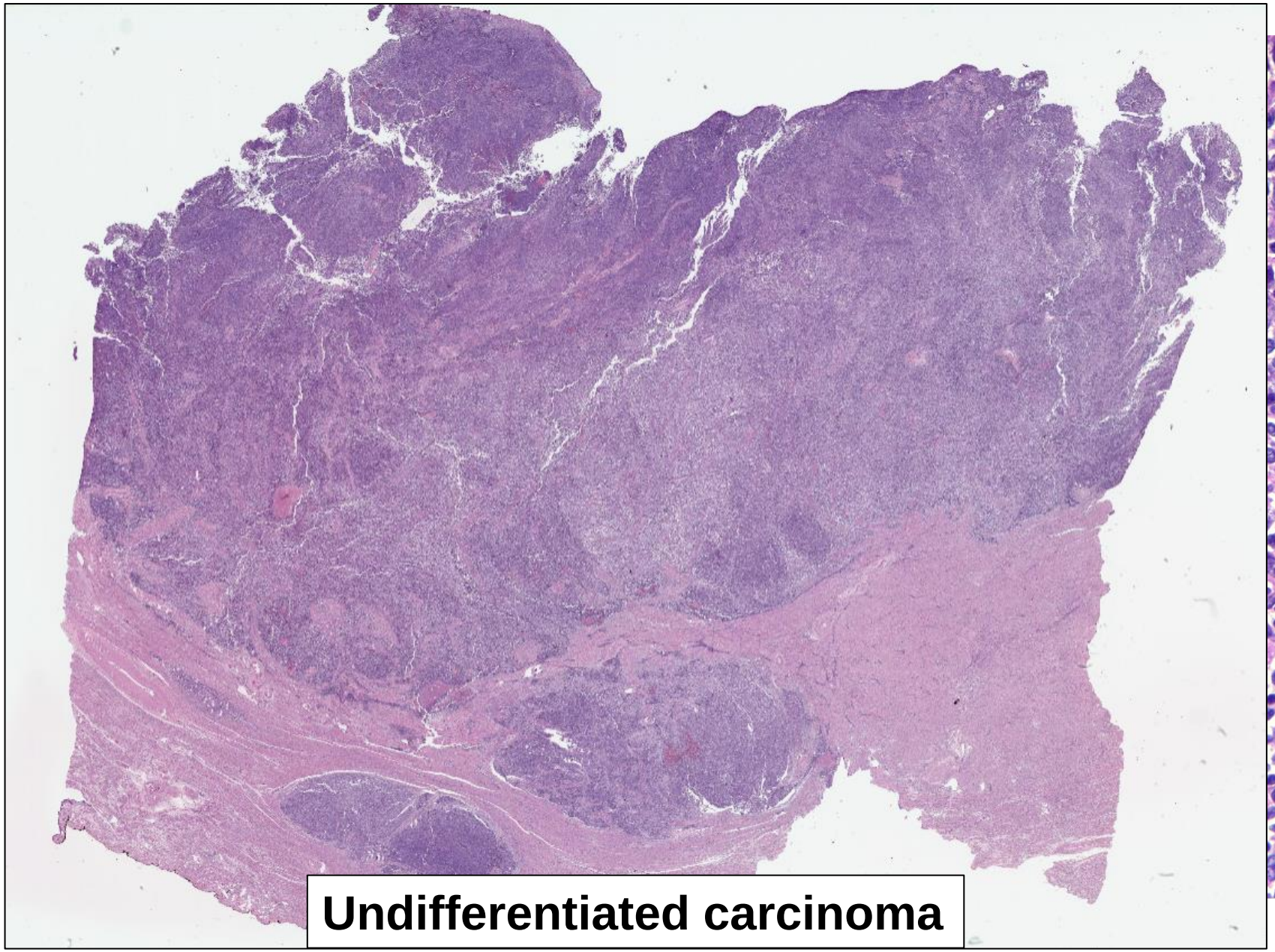




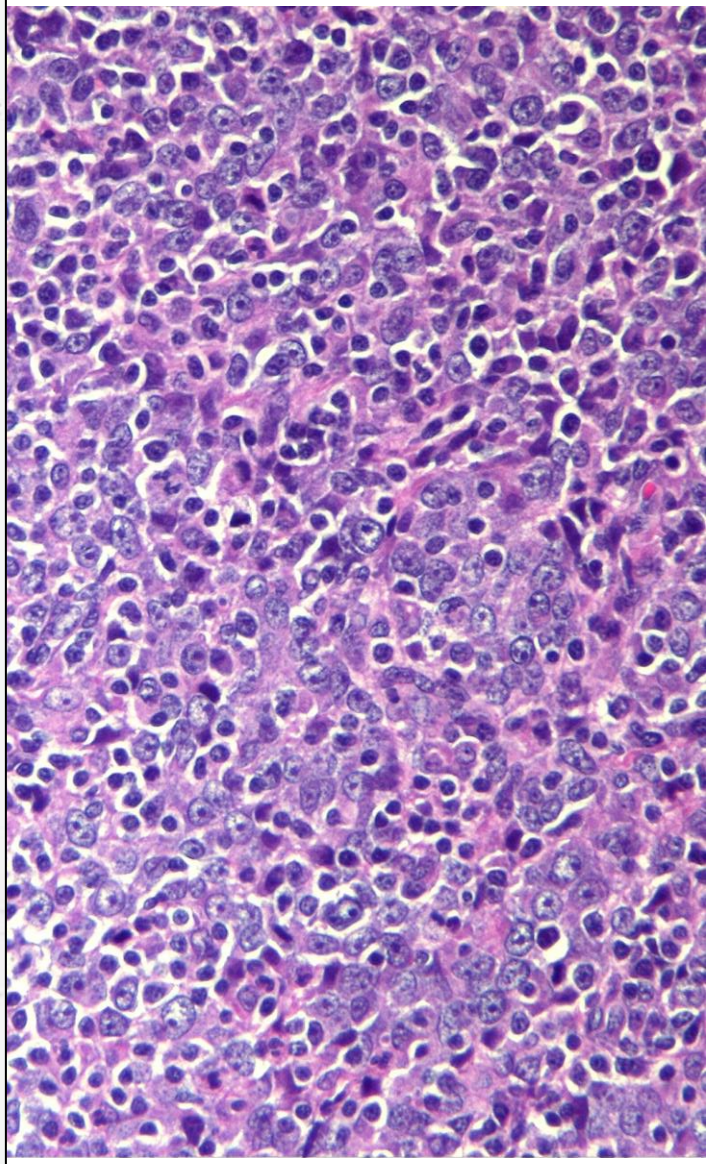


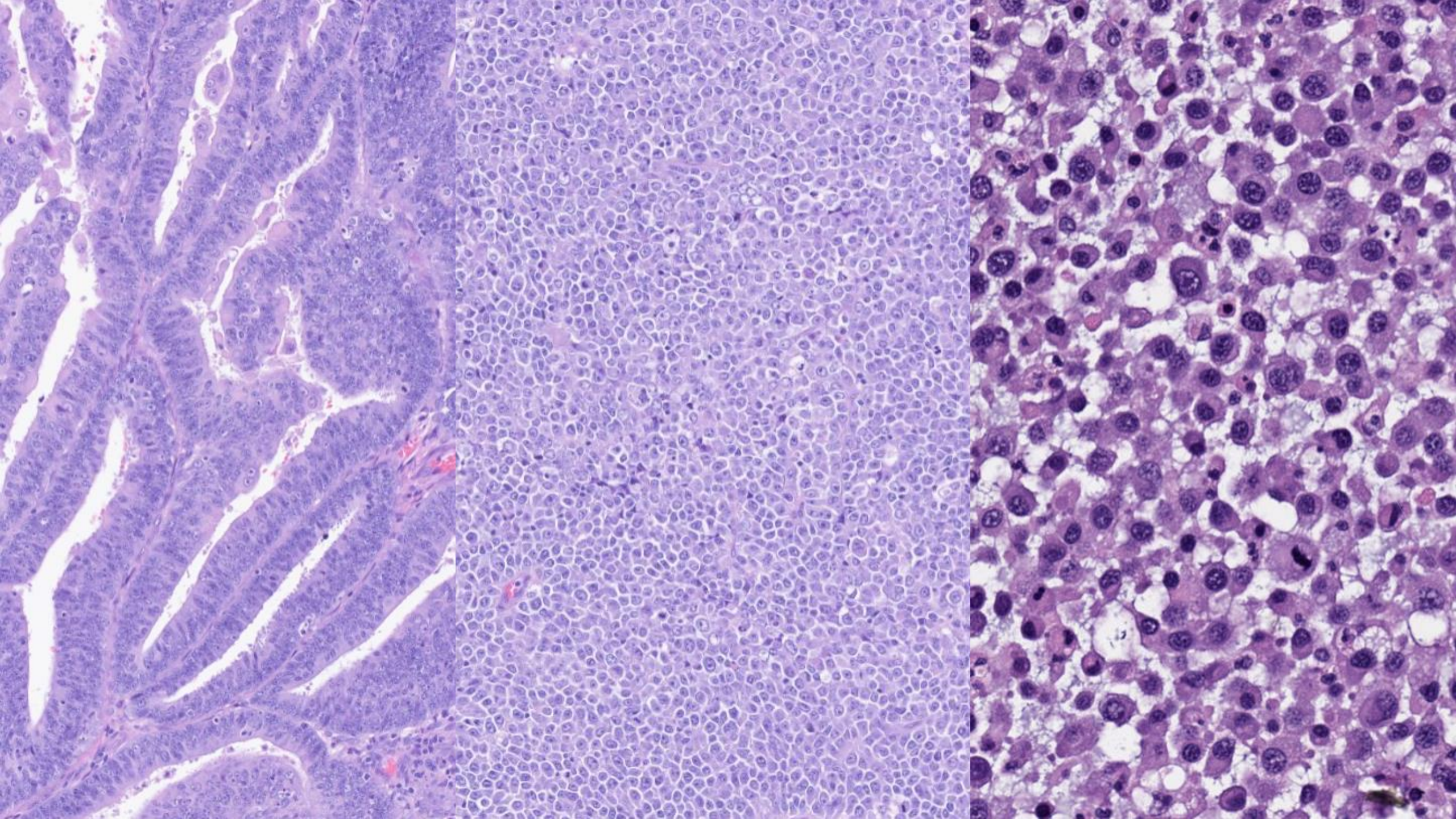


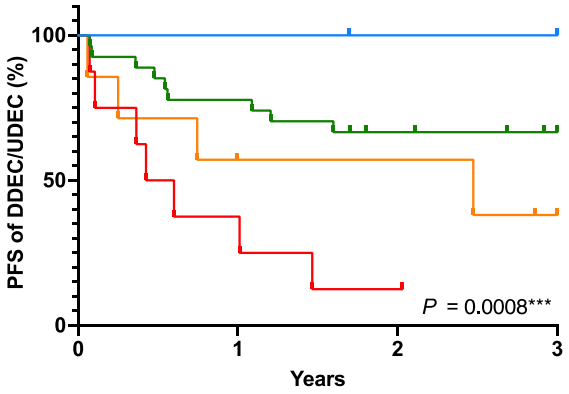
Positive EMA (patchy)
Negative PAX8
Negative CK7
Negative E-cad



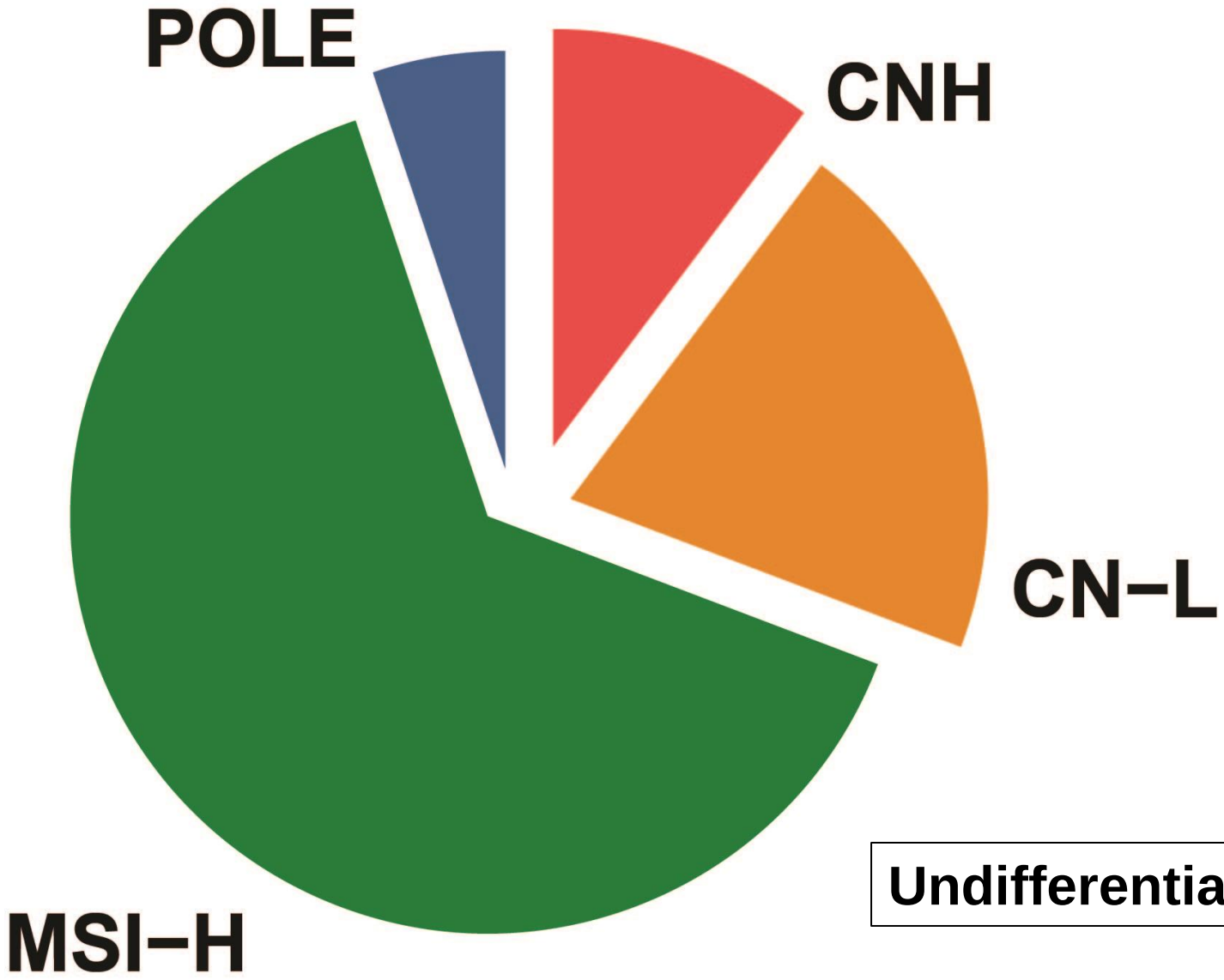
Undifferentiated carcinoma







Howitt BE and Hammer PM, unpublished data



Undifferentiated carcinoma

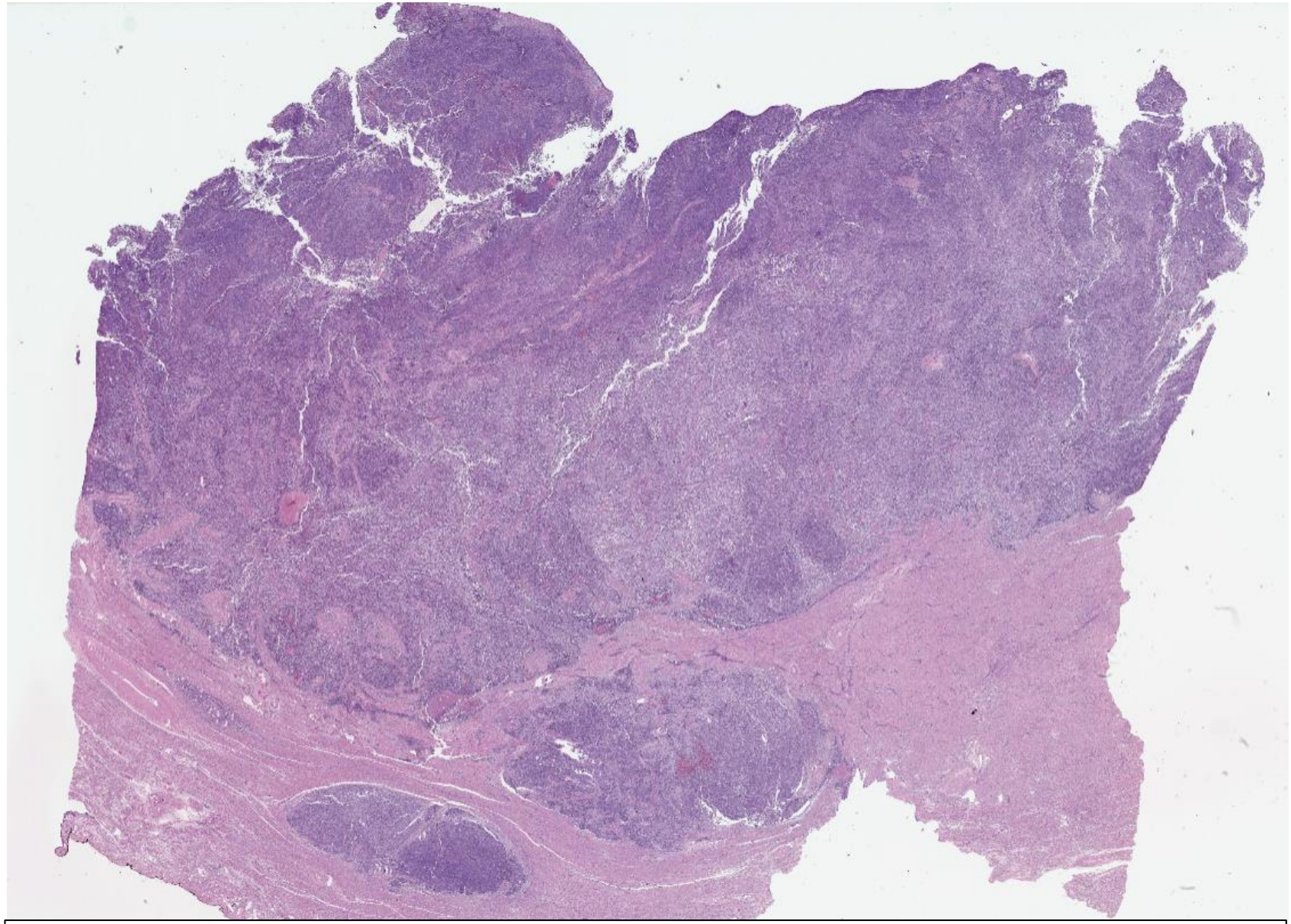
Summary	29 mutations, 1 copy number alteration, no structural variants detected. 3 alterations have OncoKB treatment interpretations.
MSI Status	MICROSATELLITE INSTABILITY-HIGH (MSI-H). See MSI note below.[β]
Tumor Mutation Burden	The estimated tumor mutation burden (TMB) for this sample is 23.9 mutations per megabase (mt/Mb). The median TMB assessed by MSK-IMPACT for all patients is 3.9 mt/Mb and for patients with Endometrial Cancer is 6.1 mt/Mb as of the date this report was issued.
Comments	Copy number profile is suggestive of broad copy number gain on chromosome regions 11q14.2-11q24, excluding KMT2A, and 19q.

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Mutations				
PIK3CA	Missense Mutation	E545K *(c.1633G>A)*	exon 10	VAF: 45.9%
CHEK1	Frameshift Deletion	T226Hfs*14 *(c.676del)*	exon 7	VAF: 41.6%
KRAS	Missense Mutation	G12V *(c.35G>T)*	exon 2	VAF: 39.4%
ARID1A	Frameshift Deletion	P1135Cfs*57 *(c.3402_3403del)*	exon 12	VAF: 34.4%
ARID1A	Nonsense Mutation	M1634* *(c.4899del)*	exon 18	VAF: 32.8%
CIC	Missense Mutation	R1515C *(c.4543C>T)*	exon 20	VAF: 2.5%
MAP3K1	Missense Mutation	S1330W *(c.3989C>G)*	exon 17	VAF: 38.6%
NFE2L2	Missense Mutation	E82D *(c.246A>C)*	exon 2	VAF: 33.6%
TP53	Missense Mutation	R273H *(c.818G>A)*	exon 8	VAF: 37.7%
FUBP1	Frameshift Deletion	S11Lfs*43 *(c.30del)*	exon 1	VAF: 31.6%
KMT2B	Frameshift Deletion	P2258Lfs*3 *(c.6773del)*	exon 28	VAF: 19.1%
KMT2D	Frameshift Deletion	G1235Vfs*95 *(c.3704del)*	exon 11	VAF: 32.8%
KMT2D	Frameshift Deletion	P2354Lfs*30 *(c.7061del)*	exon 31	VAF: 38.7%
LATS1	Frameshift Deletion	F1084Lfs*44 *(c.3252del)*	exon 8	VAF: 41.0%
LATS1	Frameshift Deletion	N271Lfs*43 *(c.811_812del)*	exon 4	VAF: 42.5%
PTPRT	Frameshift Deletion	P1094Rfs*6 *(c.3281del)*	exon 24	VAF: 33.2%
TP53	Frameshift Deletion	V73Wfs*50 *(c.216del)*	exon 4	VAF: 34.3%
SETD2	Splicing Mutation	X1759_splice *(c.5277+1G>A)*	exon 10	VAF: 40.0%
FAT1	In-frame Deletion	N561del *(c.1680_1682del)*	exon 2	VAF: 36.9%
SCG5	In-frame Deletion	V196del *(c.587_589del)*	exon 6	VAF: 34.0%

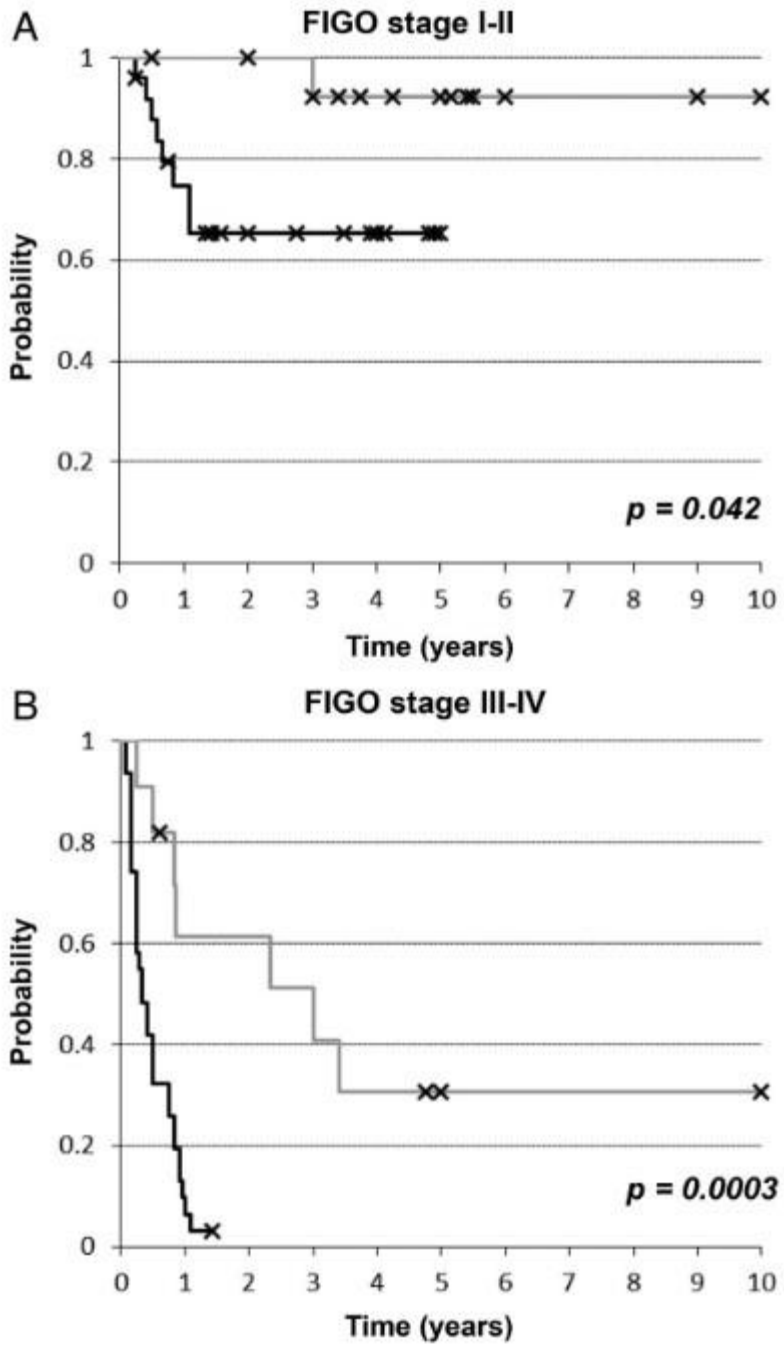
Chr:Pos	Ref	Alt	Gene	Exon	TxID	cDNA	AA	Variant Class
19:11097624	GC	G	SMARCA4	exon5	NM_001128849	c.810delC	p.M272Cfs*31	Frame_Shift_Del
19:11098424	GC	G	SMARCA4	exon6	NM_001128849	c.947delC	p.P316Lfs*10	Frame_Shift_Del

SMARCA4	Missense Mutation	M527I *(c.1581G>A)*	exon 9	VAF: 40.9%
ZFHX3	Missense Mutation	A884T *(c.2650G>A)*	exon 2	VAF: 33.3%



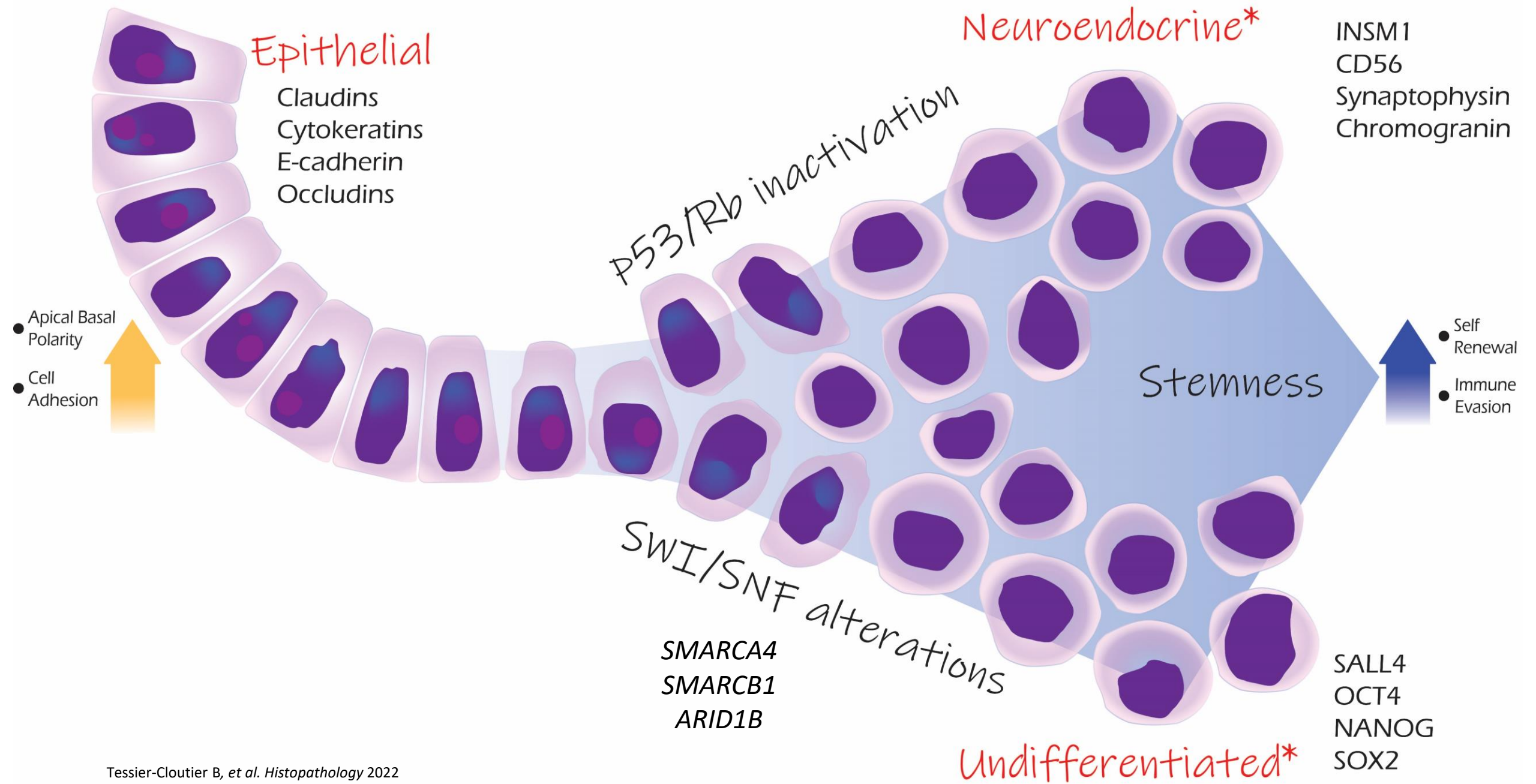
Positive EMA (patchy)
Negative PAX8
Negative CK7
Negative E-cad

MMRd undifferentiated carcinoma, MMR and SMARCA4-deficient



SMARCA4-deficiency

Tessier-Cloutier B*, et al. J Pathol Clin Res* 2021

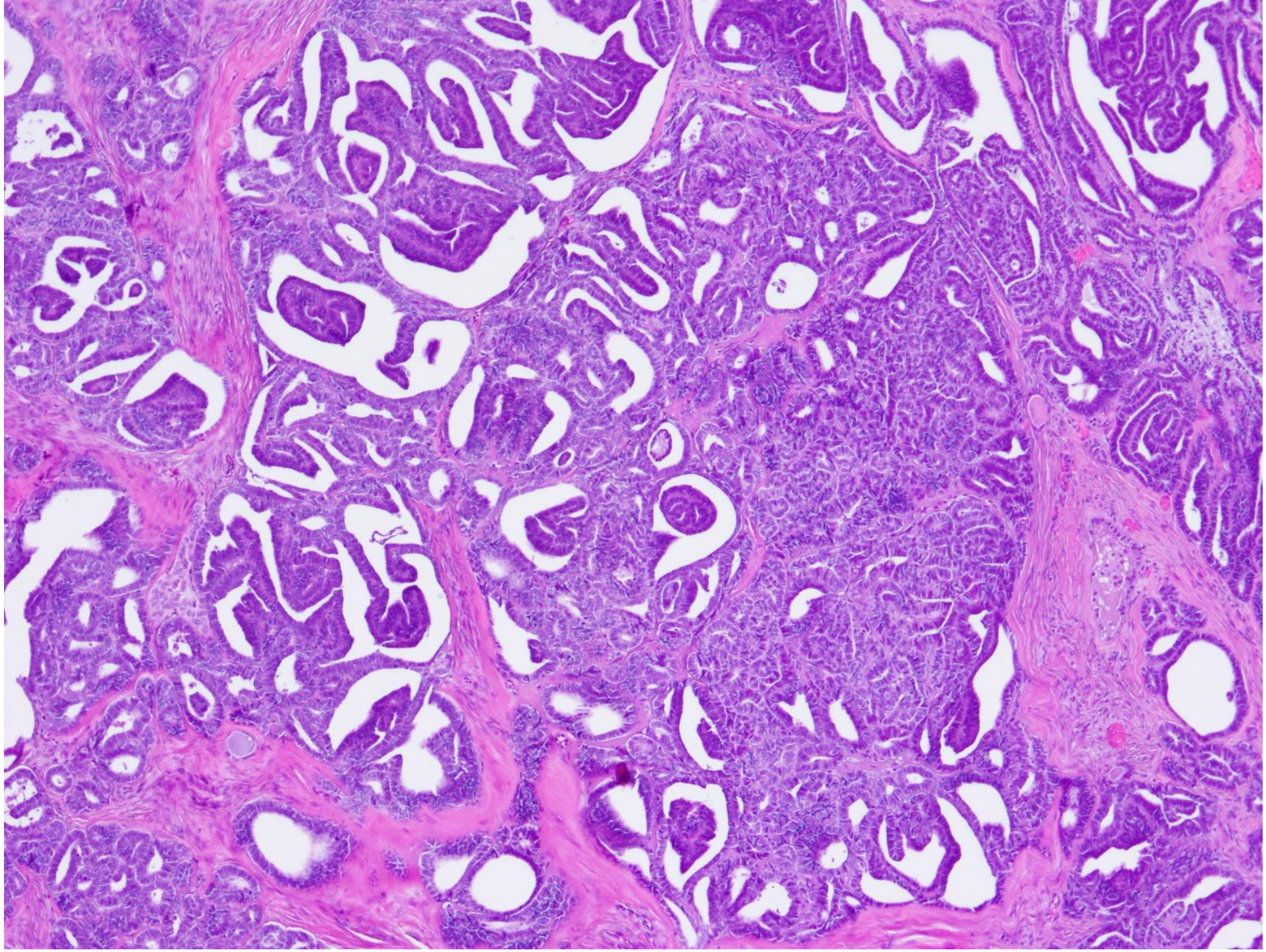


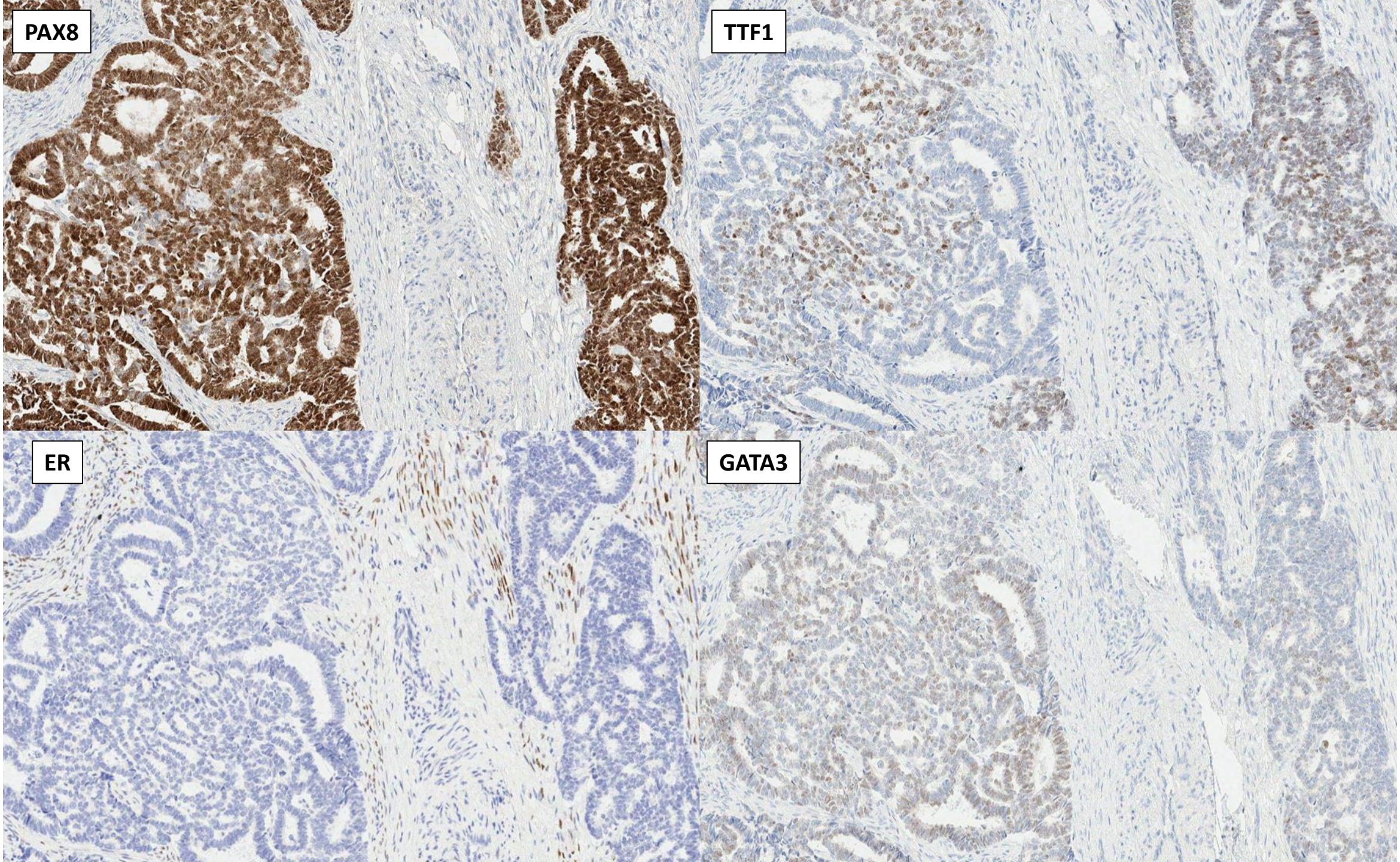
Tessier-Cloutier B*, et al. Histopathology* 2022

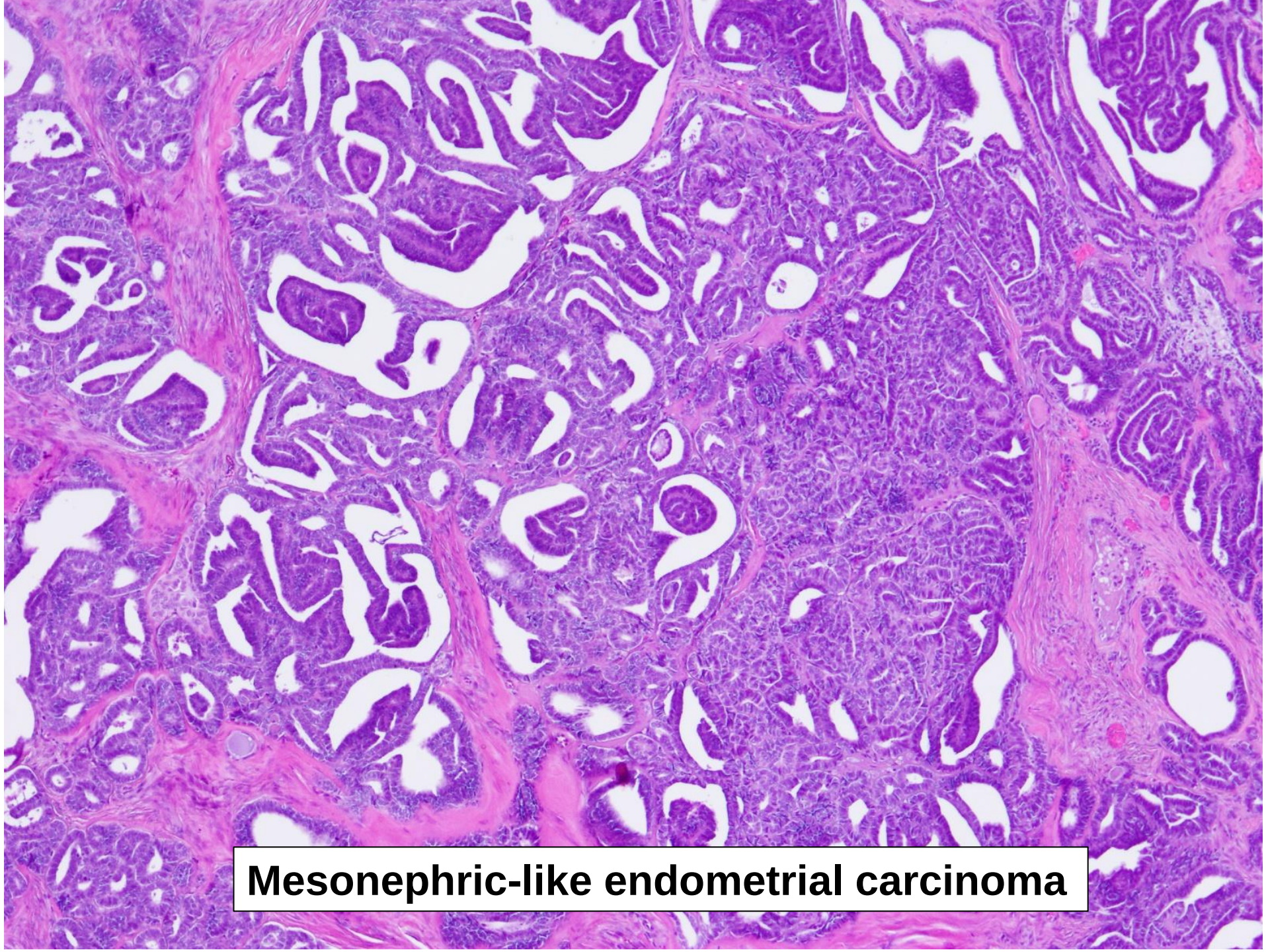
* Can co-exist in the same tumor/cell

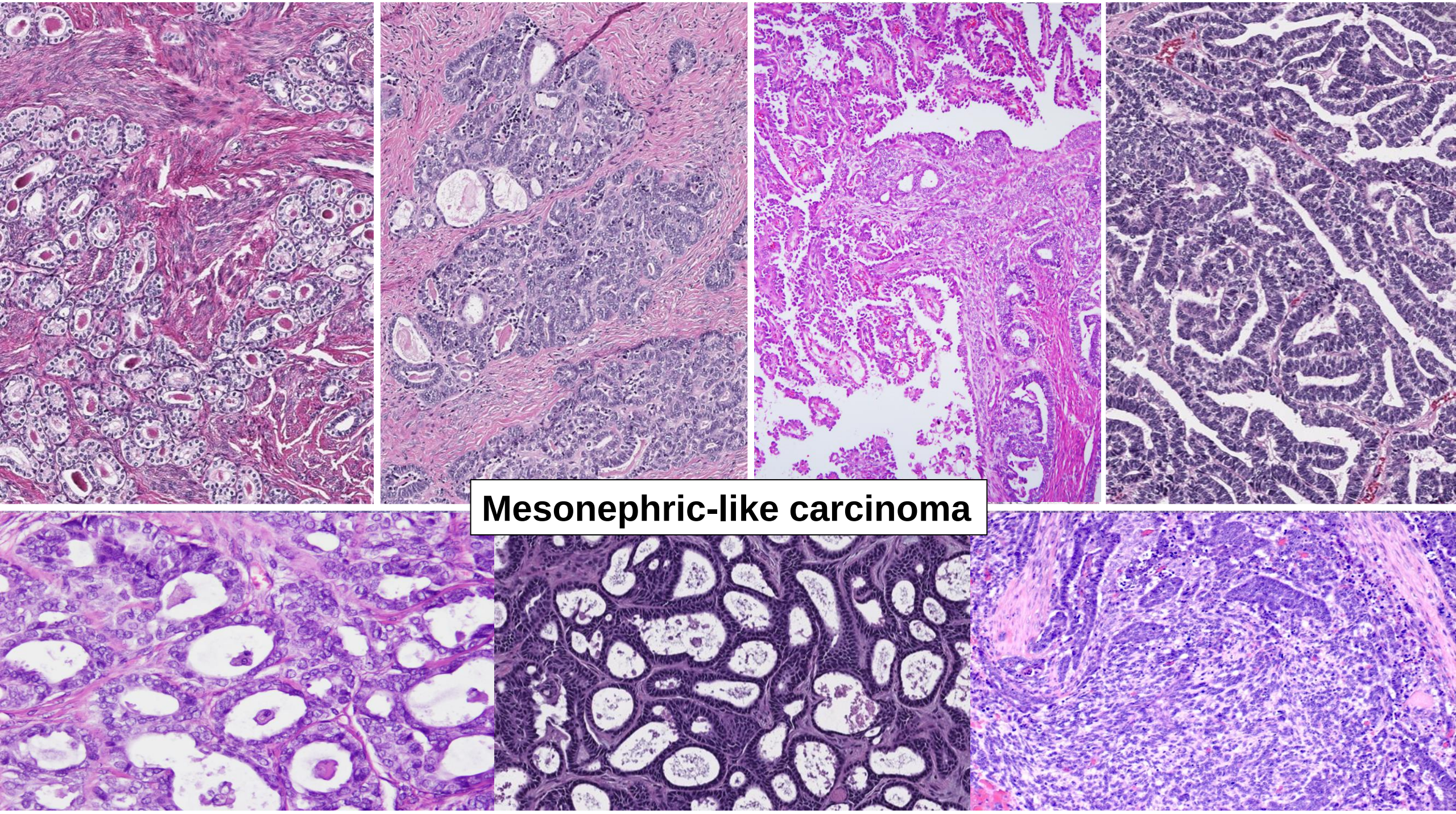
Case presentation

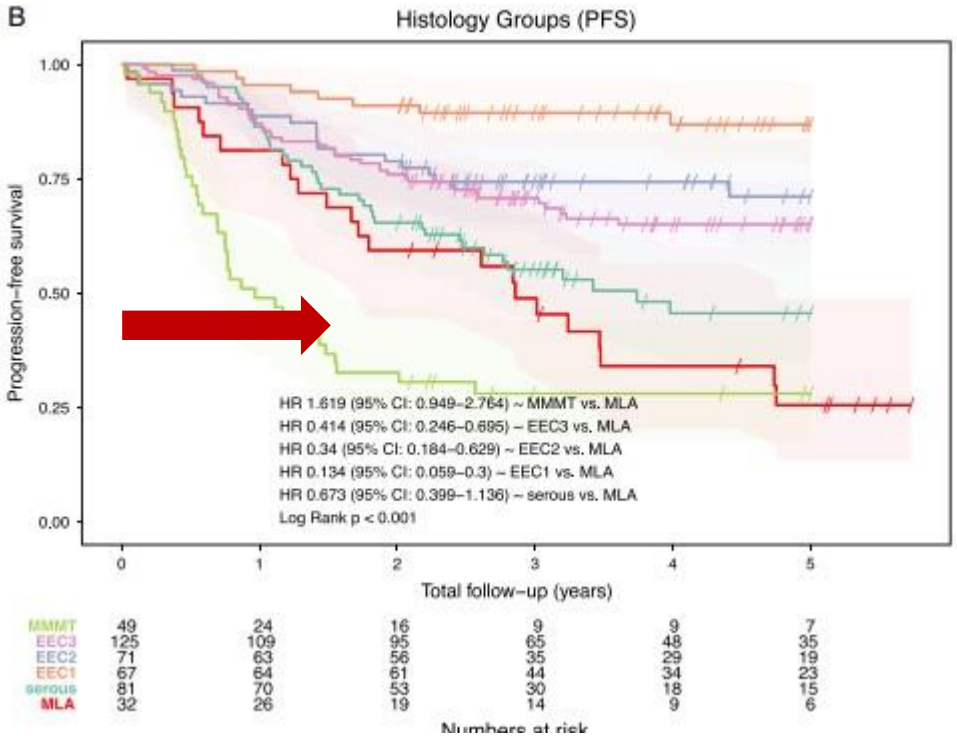
- 58 year-old patient
- FIGO stage IVC (2023) with pulmonary metastasis




PAX8
TTF1
ER
GATA3

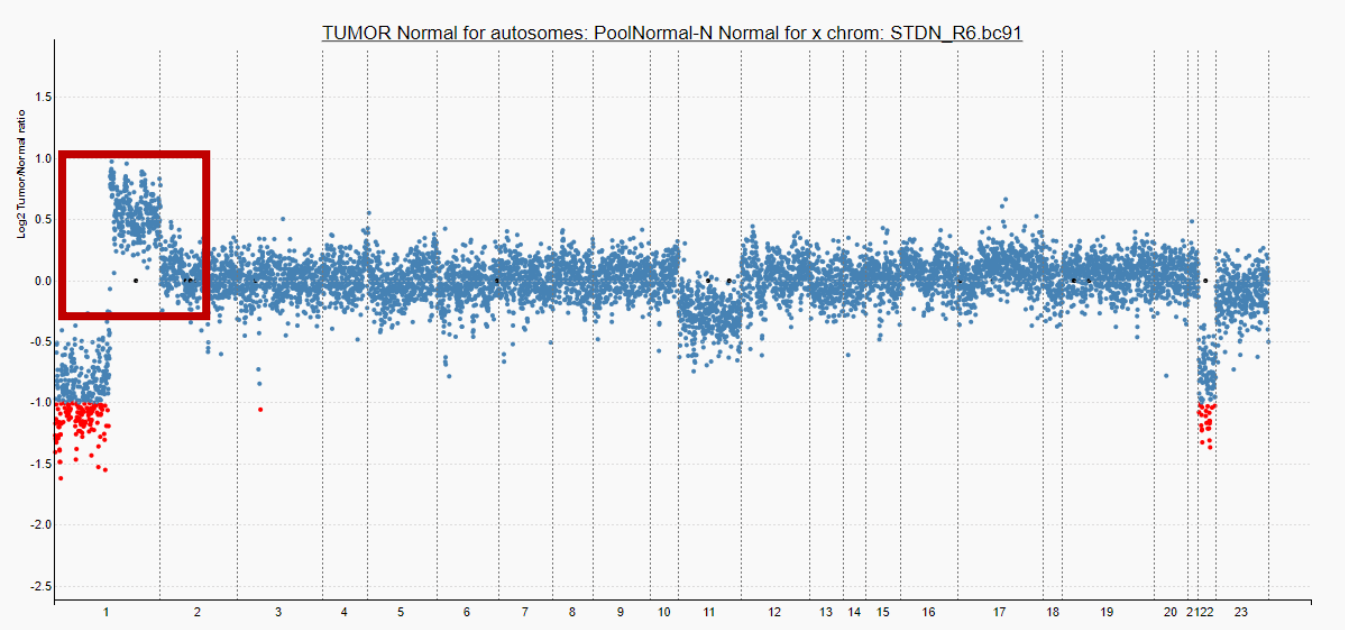

Mesonephric-like endometrial carcinoma


Mesonephric-like carcinoma

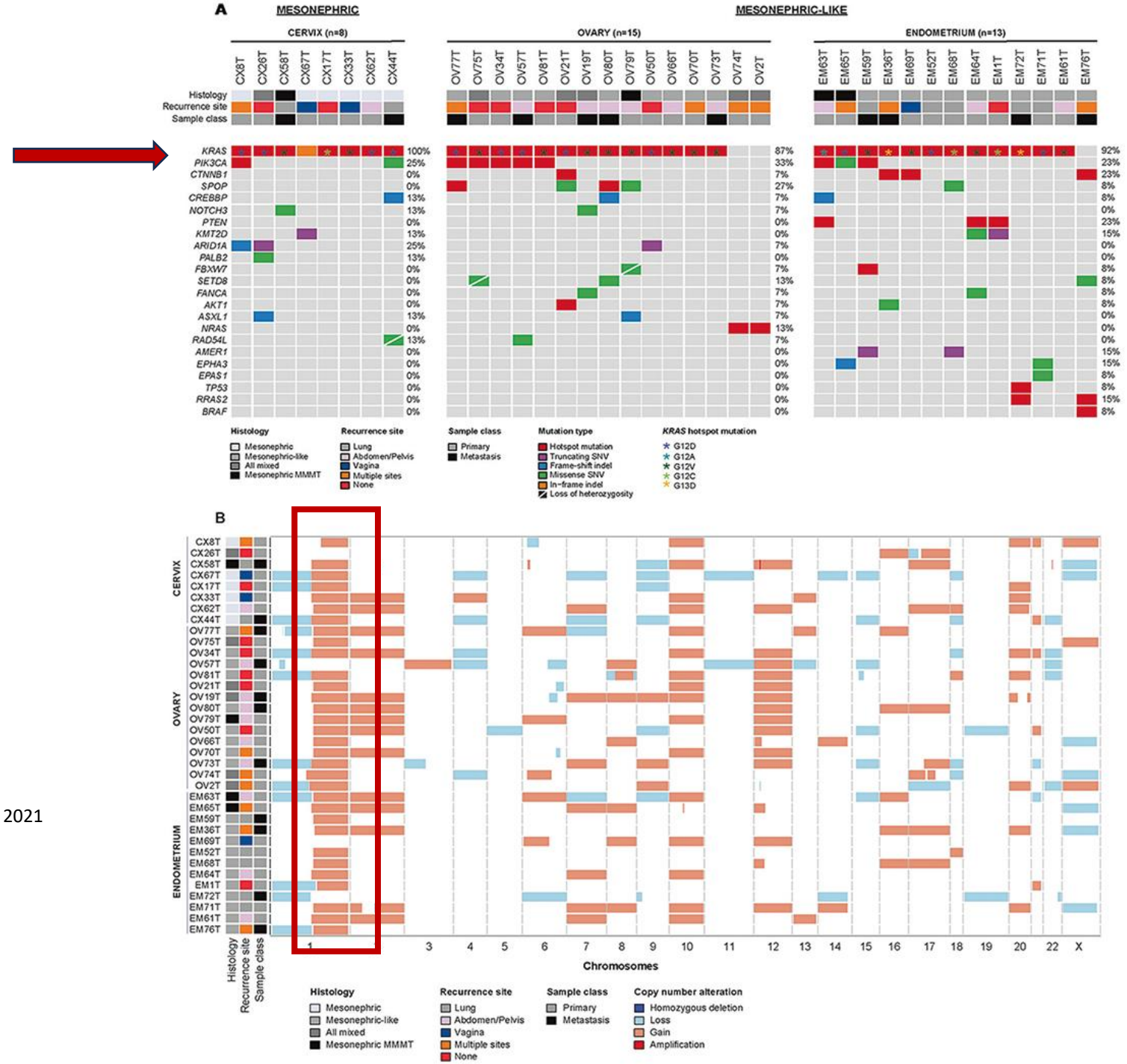


CNL

Pors J, *et al*. *Am J Surg Pathol* 2021



Chr:Pos	Ref	Alt	Gene	Exon	TxID	cDNA	AA	Variant Class	dbSNP	Method	MAF	VF_N	DP_T	AD_T	VF_T (0.33728)
12:25398284	C	A	KRAS	exon2	NM_033360	c.35G>T	p.G12V	Missense_Mutation		M V		0.0	930	494	0.53118
3:41266113	C	T	CTNNB1	exon3	NM_001904	c.110C>T	p.S37F	Missense_Mutation		M V		0.0	507	171	0.33728
12:57865657	C	A	GLI1	exon12	NM_005269	c.3134C>A	p.T1045N	Missense_Mutation		M V		0.0	1547	469	0.30317



da Silva, E.M., *et al. Mod Pathol* 2021

Clinico-pathological summary

- POLE:
  - Very low risk regardless of histotype and grade
- MSI-H:
  - Low risk with MMR mutation
  - Intermediate risk across histotypes and grades with *MLH1* promoter methylation
  - Very high risk with *SMARCA4/ARID1B* mutation
- NSMP: risk is associated with histotype, grade and molecular subtype
  - Low risk if low-grade endometrioid, low stage and ER+
  - High risk for high-grade endometrioid and clear cell
  - Very high risk for mesonephric-like, carcinosarcoma and with *SMARCA4/ARID1B* mutation
- CN-H
  - High risk for serous, clear cell and endometrioid
  - Very high risk for carcinosarcoma, divergent differentiation and with *myc* amplification

Take home messages

- PROMISE algorithm is essential
- *POLE* testing is strongly recommended for “aggressive histotypes” confined to uterus
- Conventional therapeutic targets
  - MSI-H (checkpoint inhibitors)
  - CN-H *Her2+* (Her2 inhibitors)
- Unconventional therapeutic targets
  - *RAS* pathway inhibitors
  - *AKT* inhibitors
  - EZH2 inhibitors (*SMARCA4* in peds)….

2020 Harlan J. Spjut Award Recipient

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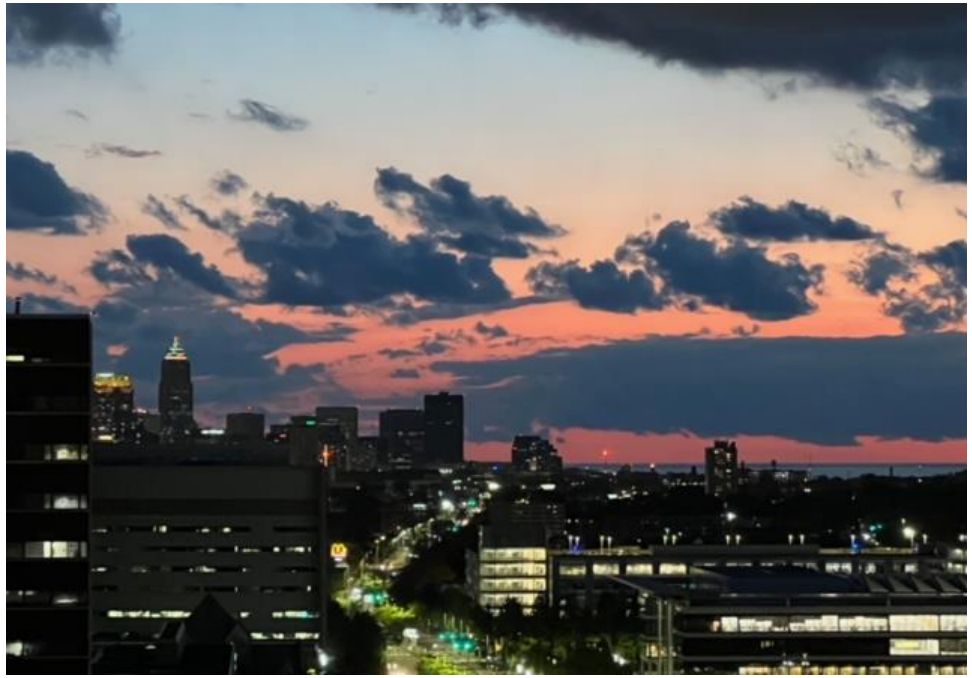
Anais Malpica, MD

My dear friend



Come and visit me on Lake Erie

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Thank you for your interest