Molecular Subtypes of Endometrial Cancers: Approaches and Considerations for Testing

VALARIE MCMURTRY, MD, PHD

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Objectives

1

- Understand the reasoning and rational for developing a molecular based classification of endometrial cancers

2

- Select correct testing and order of testing for clinical situations

3

- Describe the testing considerations for each molecular classification

4

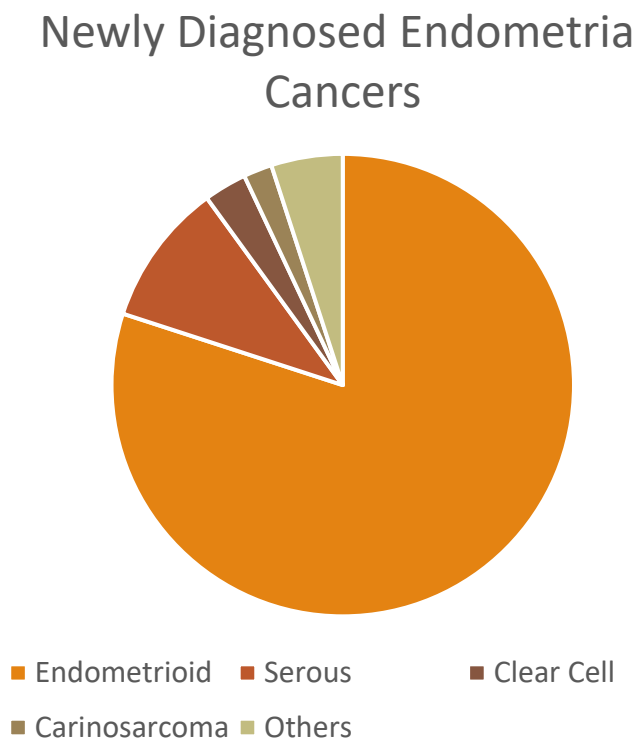
- Understand the recurrent genetic alterations for the molecular classifications

Endometrial cancer

Endometrial cancer is increasing in incidence and mortality

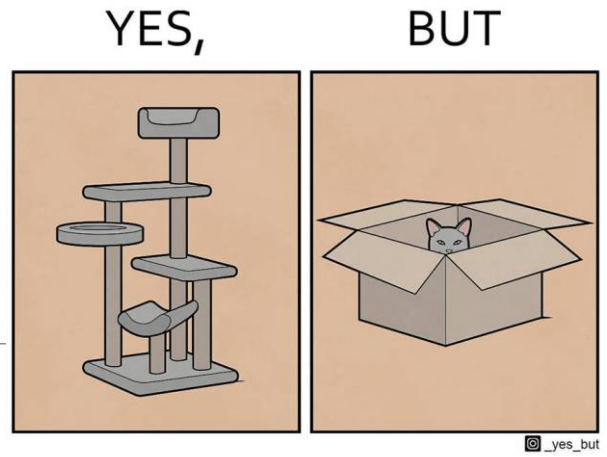
Survival has not increased for the last 4 decades

“In 2013, National Institutes of Health (NIH)-directed funding for EC was $14 million compared with $631 million for breast cancer research. Our understanding of this disease lags far behind other cancers; and, for decades, there has been very little change in the approach to EC from what our grandmother would have been offered” – McAlpine et al



PMID: 36633525, 27308732

Prognostic differentiation



YES,

Bokhman (1983): type I and type II endometrial cancer
- Type I: estrogen driven, low-grade
- Type II: estrogen independent, high-grade, biologically aggressive

Histotype

Disease grade

FIGO stage

Presence of lympho-vascular space invasion

Deep myometrial invasion

BUT…

~20% of women with type I endometrial cancer experience a relapse while ~50% of those with type II do not

Histological subtype and grade have poor reproducibility even amongst expert pathologists

FIGO stage and LVSI are only available post-hysterectomy

Artist: Anton Gudim
PMID: 23629444, 29190319

Objectives of molecular classification

A validated risk-stratification model that accurately defines risk of disease recurrence and death will guide clinical care by allowing for treatment de-escalation for those at lowest risk and intensification for those at high risk

- Optimal follow up to monitor for recurrence
- Primary treatments for selected types

Private Information

2013

Integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas

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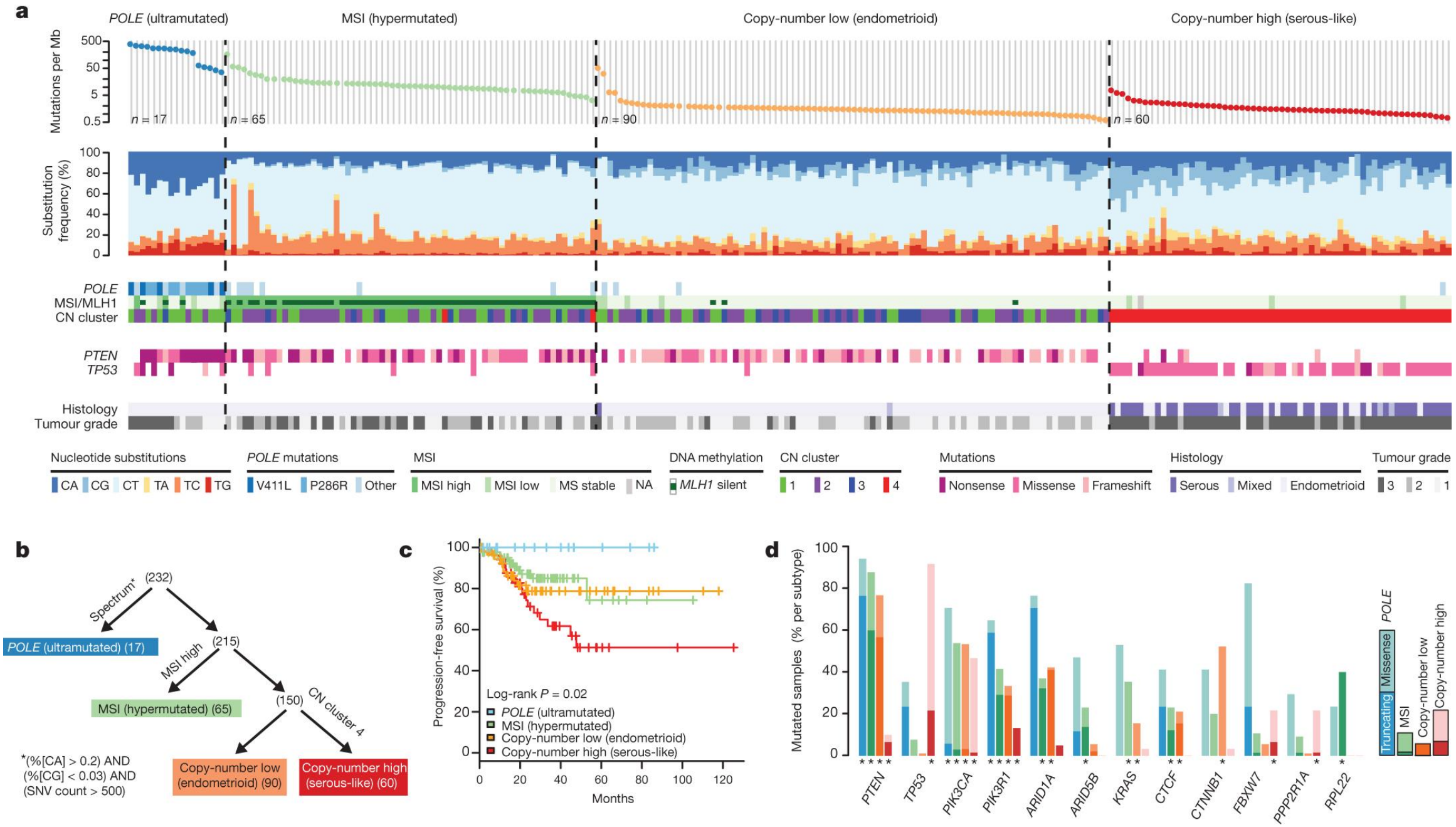


PMID: 23636398

PORTEC trails

Retrospective analysis of PORTEC 1 and 2 trails

- Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model

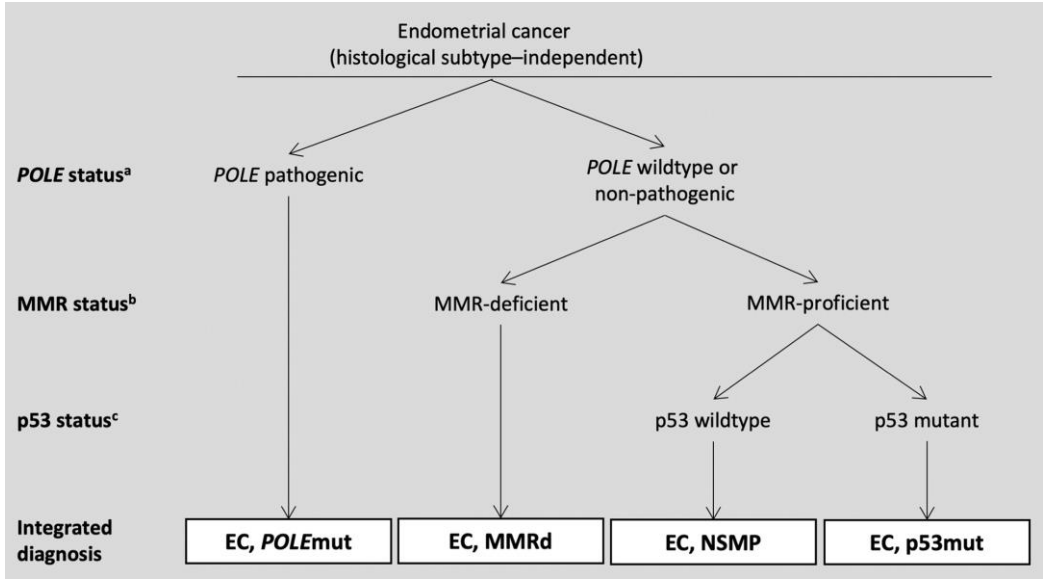
Retrospective analysis of PORTEC 3

- Molecular classification has strong prognostic value in high-risk EC, with significantly improved RFS with adjuvant CTRT for p53abn tumors, regardless of histologic type. Patients with **POLE** mut EC had an excellent RFS in both trial arms.

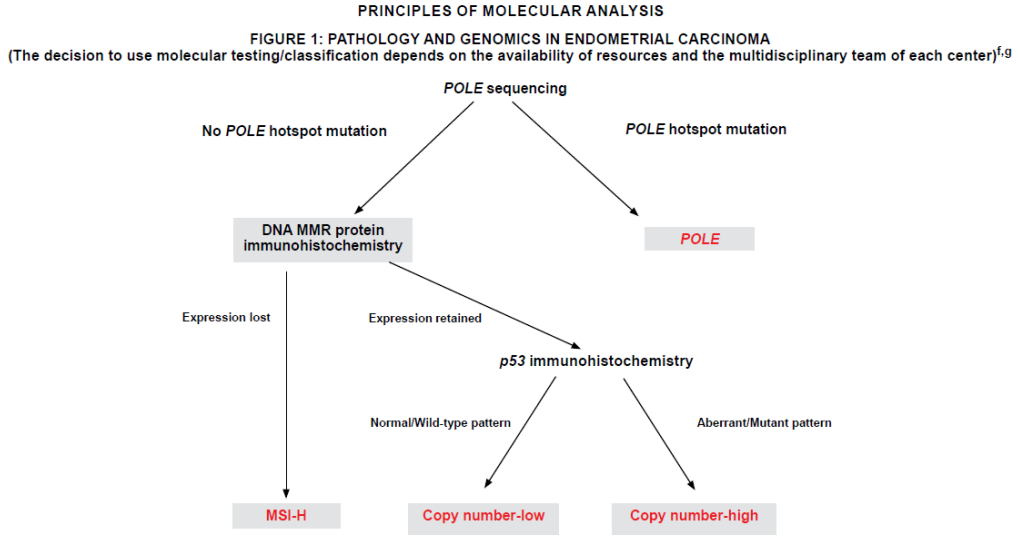
PMID: 27006490, 32749941

WHO and NCCN guidelines

WHO FEMALE GENITAL TUMORS, 5TH EDITION



NCCN GUIDANCE – V1.2024



[f] Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g] Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas.

Private Information


So, pathology, why aren’t you testing for all these things??
The rest of the TPC

Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)

PORTEC 1: post-operative pelvic external beam radiotherapy compared to no additional treatment.

PORTEC-2, Postoperative Radiation Therapy for Endometrial Carcinoma - A Multicenter Randomized Phase III Trial Comparing External Beam Radiation and Vaginal Brachytherapy

PORTEC 3: randomized phase III trial is studying chemotherapy and radiation therapy to see how well they work compared with radiation therapy alone in treating patients with high-risk, stage I, stage II, or stage III endometrial cancer.

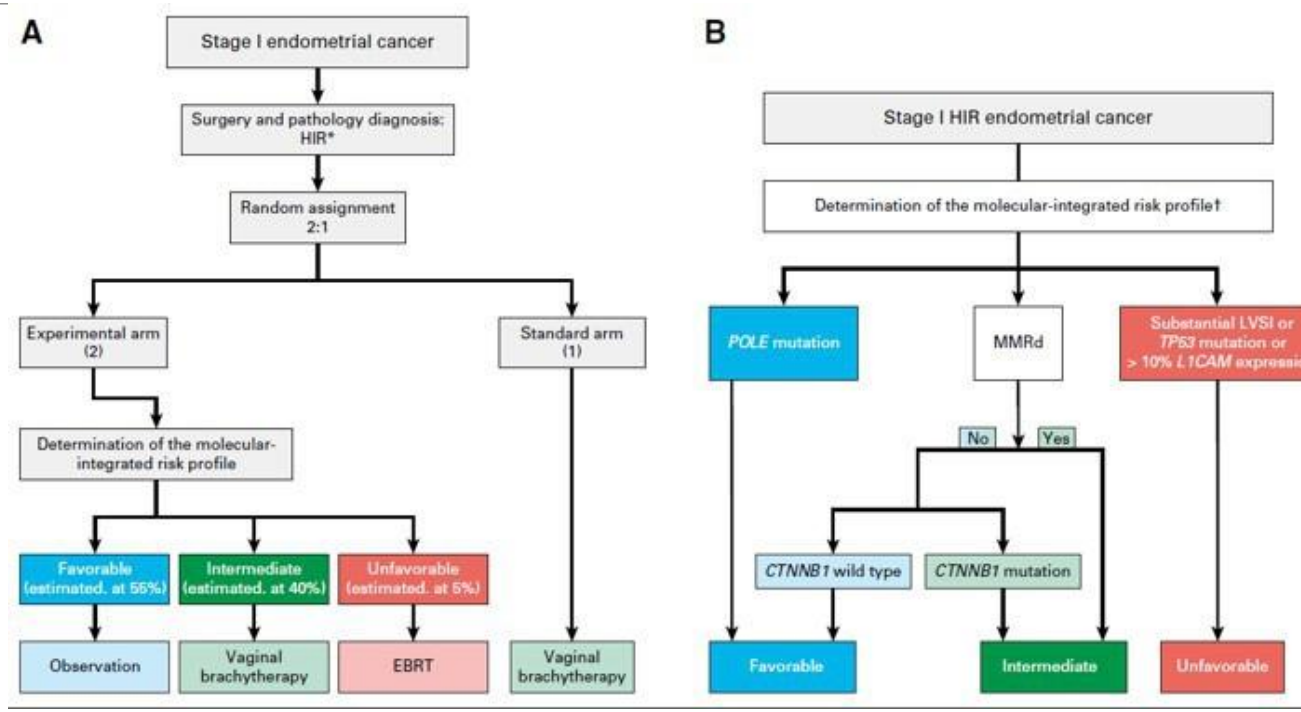
PORTEC 4a

Data coming soon!
?
¯_(ツ)_/¯

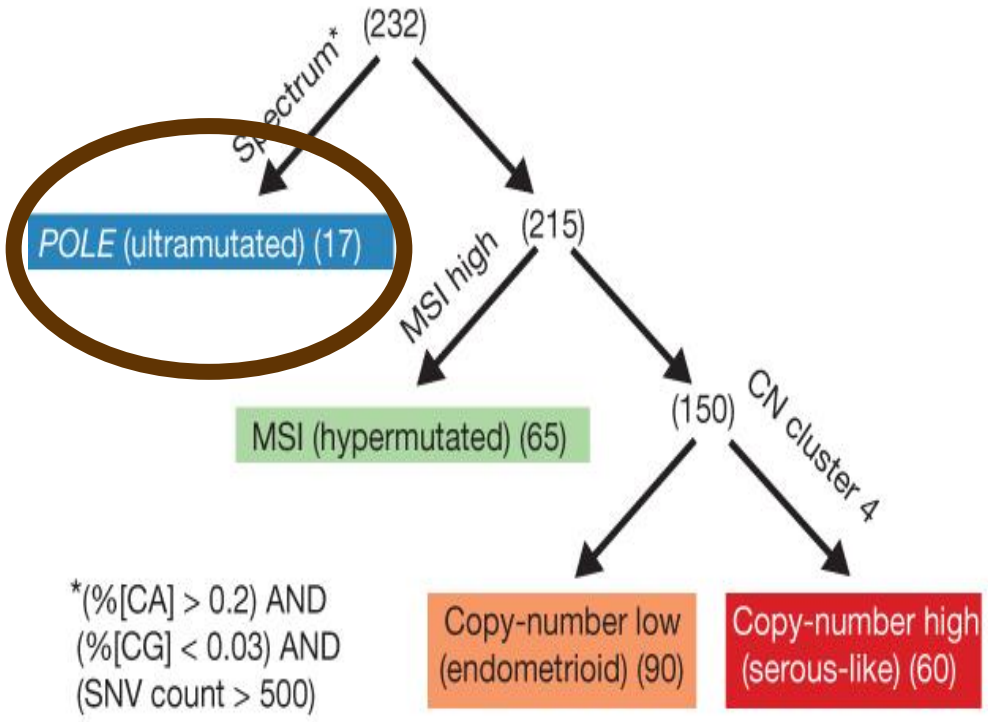
PORTEC 4a: Randomized Phase III Trial of Molecular Profile-based Versus Standard Recommendations for Adjuvant Radiotherapy for Women With Early Stage Endometrial Cancer

First trial to introduce molecular factors in the adjuvant treatment of endometrial cancer

- Omitting treatment in cases of favorable molecular profiles is safe and effective



PMID: 30078506, 33046573

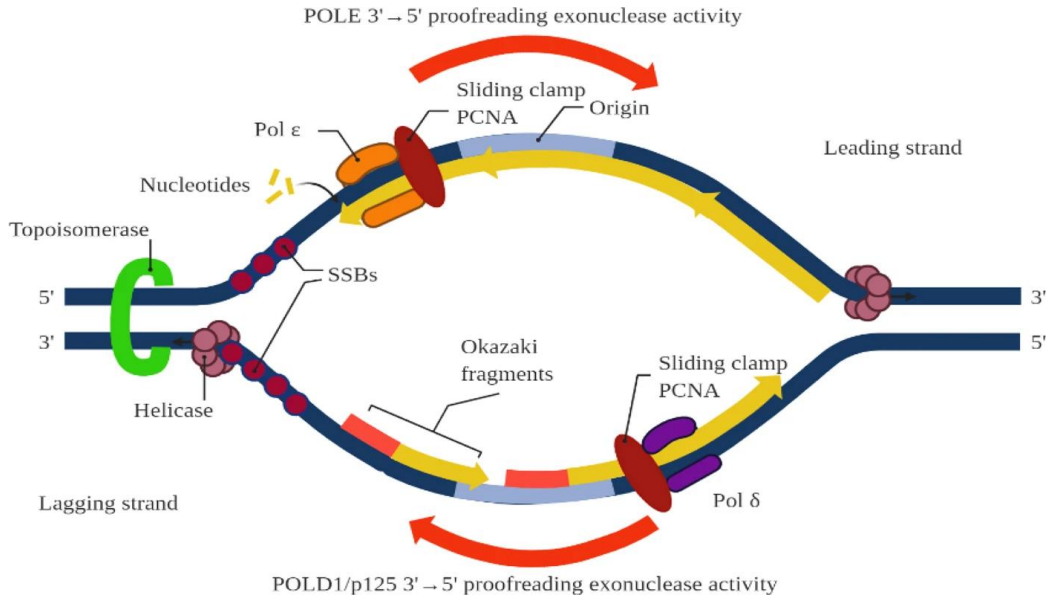

(232)
Spectrum*
POLE (ultramutated) (17)
(215)
MSI high
MSI (hypermutated) (65)
(150)
CN cluster 4
Copy-number low (endometrioid) (90)
Copy-number high (serous-like) (60)
*(%[CA] > 0.2) AND (%[CG] < 0.03) AND (SNV count > 500)

POLE

Mechanism

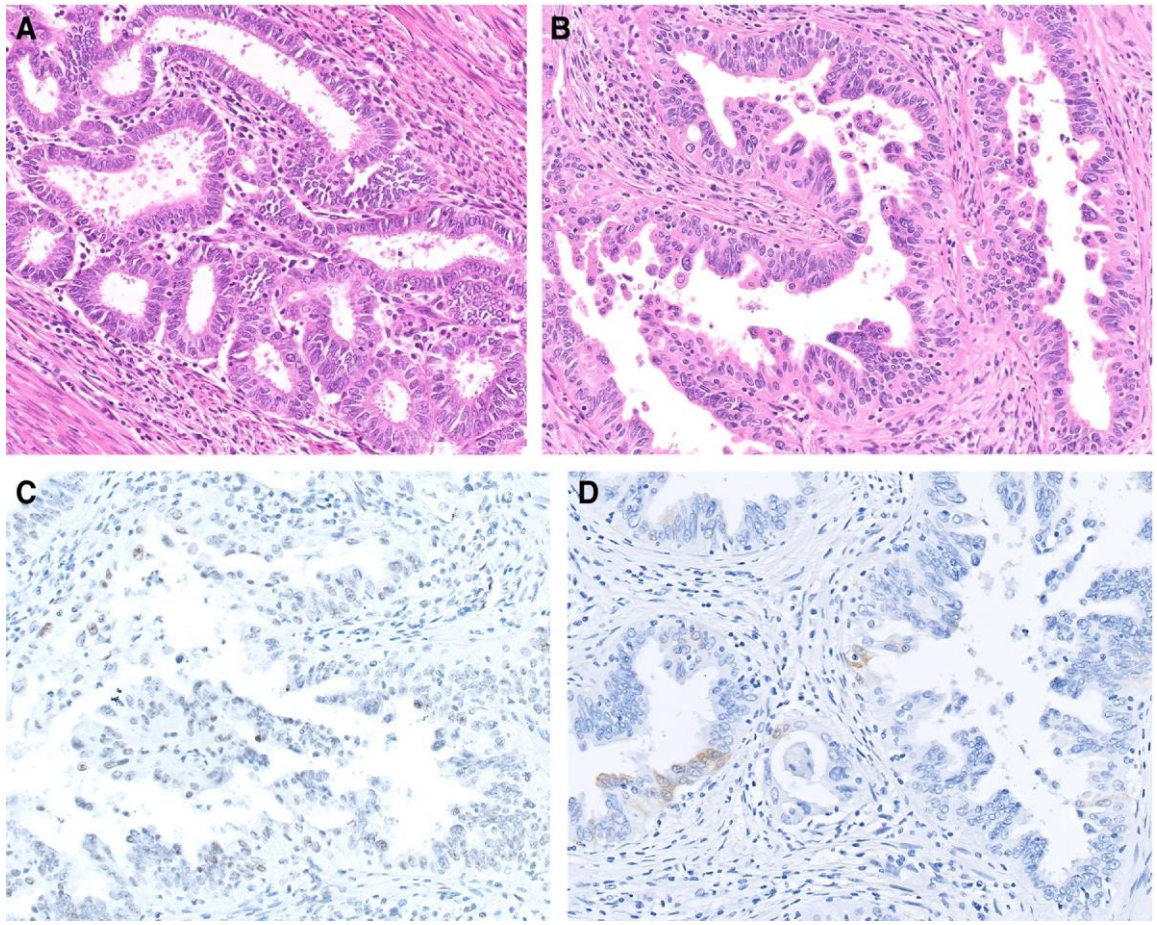
DNA proof-reading function

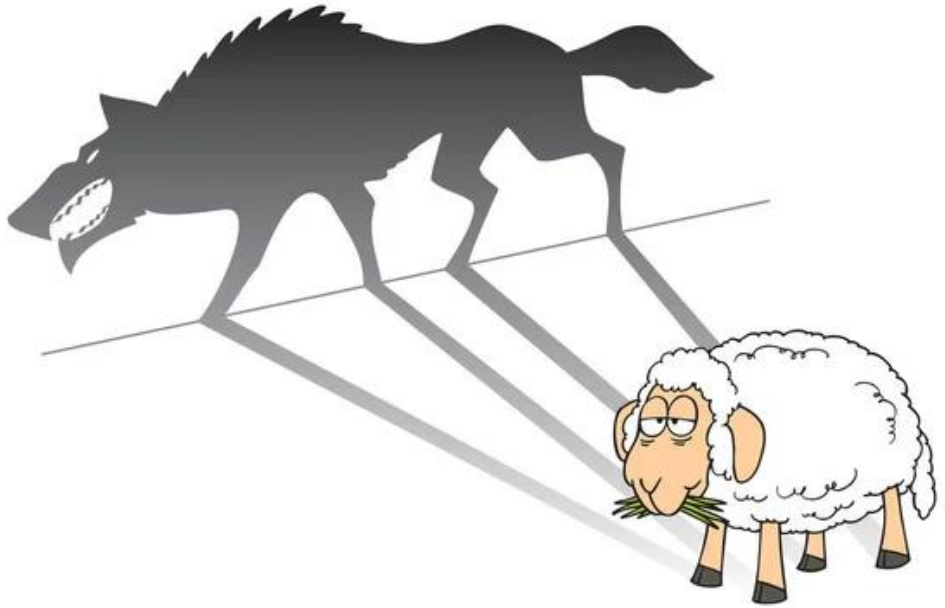
- POLE encodes the major catalytic proofreading subunits of the PolƐ DNA polymerase enzyme complex and PolƐ enzyme complex synthesizes the leading strand
- Exonuclease function locates and replaces erroneous bases in the daughter strand through failed complementary pairing with the parental strand
- Exonuclease domain mutations increase spontaneous mutation rates (mouse models)



PMID: 34363023

POLE mutation and histology





PMID: 28795426

https://www.everypixel.com/q/wolves-sheep

Should we test based on morphology?

MORPHOLOGY/IHC

Prominent immune infiltrate:

- Peritumoral or infiltrating lymphocytes

Giant cells

Focal Serous-like features

p16 unhelpful

Grade not significantly different

BOOLEAN MODELING

Sensitivity of 80% and specificity of 88%, assuming prevalence of 7%, PPV is 33%

- MLH1 wild-type expression OR p53 wild type expression
- Endometrioid-type EC
- Peritumoral lymphocytes OR tumor grade 3

Private Information

PMID: 28795426

Sequencing

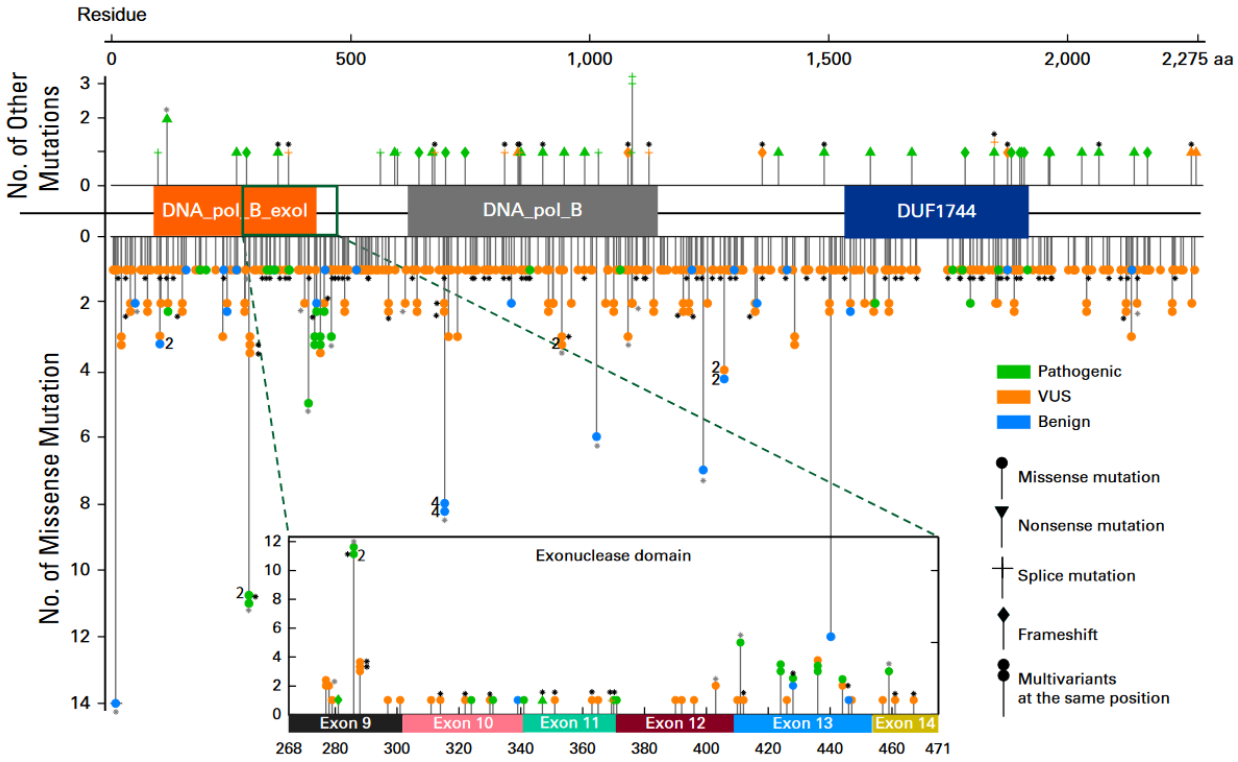
Majority of studies showing prognosis are based on

Expensive/insurance may only reimburse once

Slow TAT

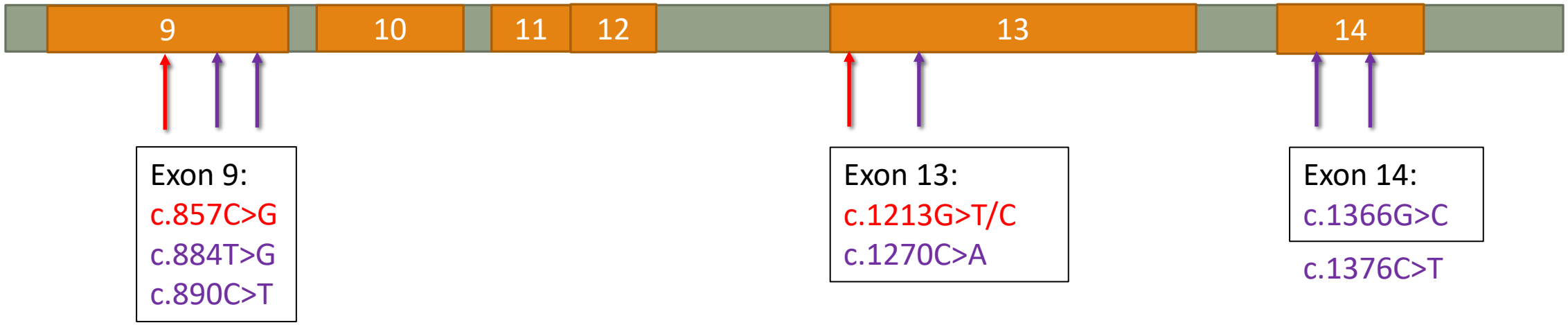
Not all alterations in POLE are related to prognosis or even clearly pathogenic (n=458, all cancers)

- 15% Pathogenic – showed prognostic significance, response to immune checkpoint inhibitor
- 16% Benign
- 69% Variant of unknown significance



PMID: 35108036

Exonuclease domain



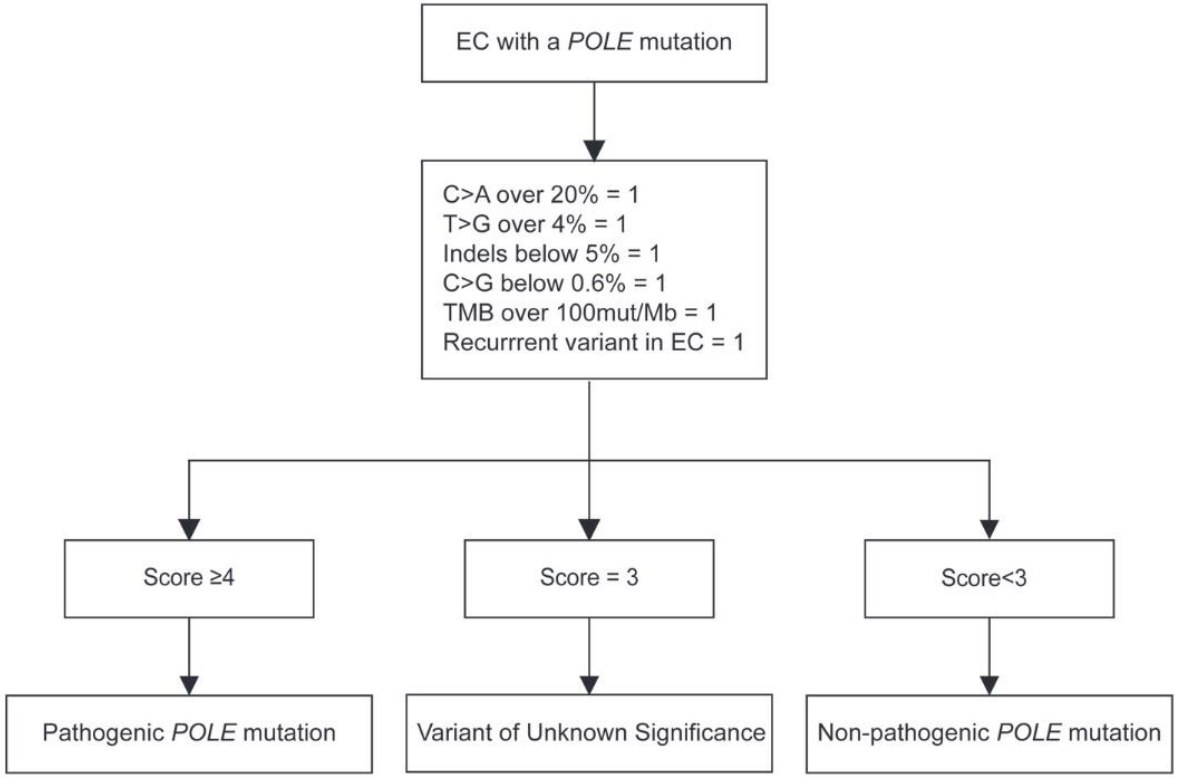
Exons

Red: 2 most common alterations

Purple: <10% of alterations

PMID: 23636398, 34910396

Scoring System for novel Mutations in POLE



*database searches

Private Information

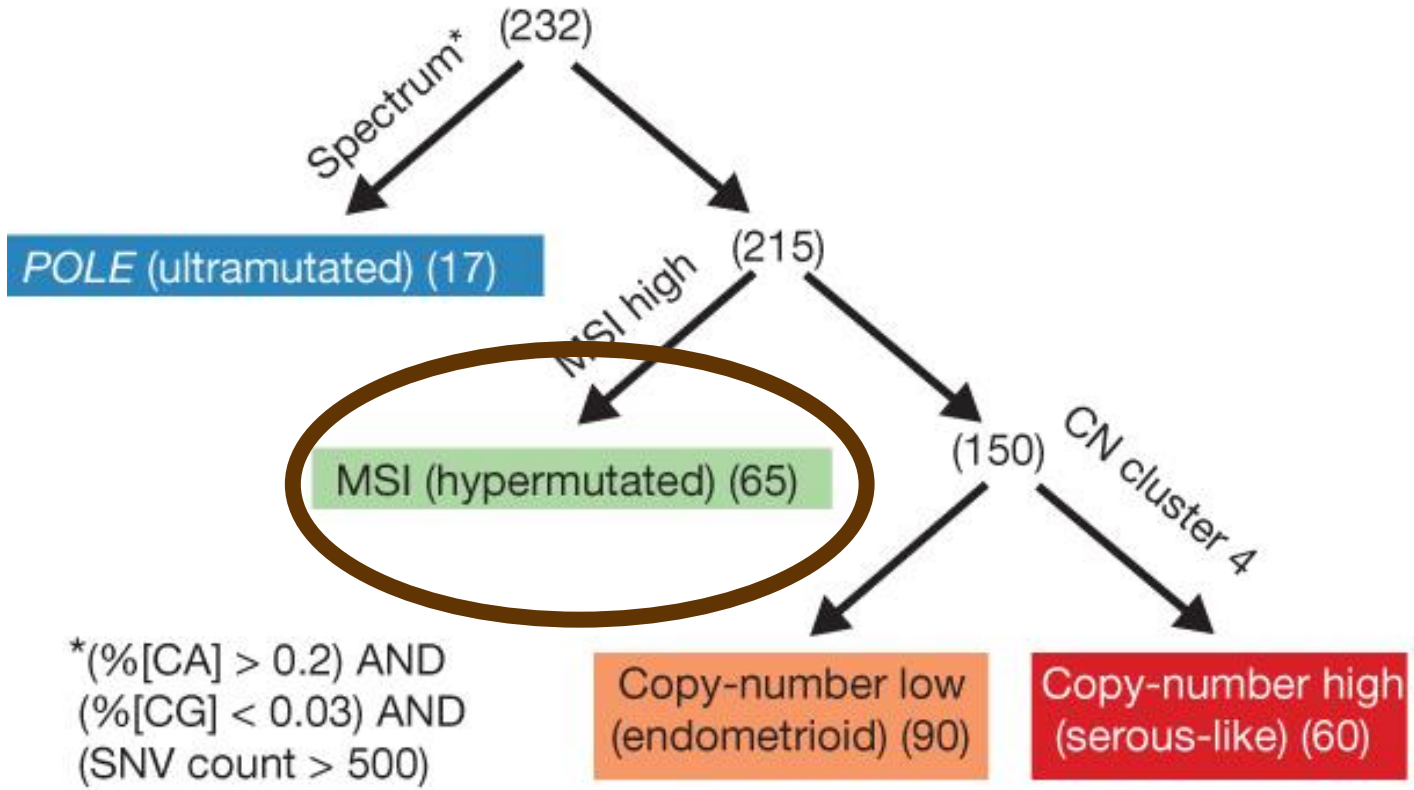
PMID: 31829442

ISGyP 2020 Annual Meeting

"Although treatment implications are suggested by several clinical trials, these cannot be incorporated into routine clinical practice in the absence of prospective data from randomized controlled clinical trials. At the present time, the purpose of classifying EC on a molecular basis, and specifically of POLE testing, is restricted to providing prognostic insight, and for treatment modulation in clinically challenging cases. This is also of diagnostic utility in young patients with p53 abnormal serous-like carcinomas."

Private Information

PMID: 33290350



Mismatch repair instability

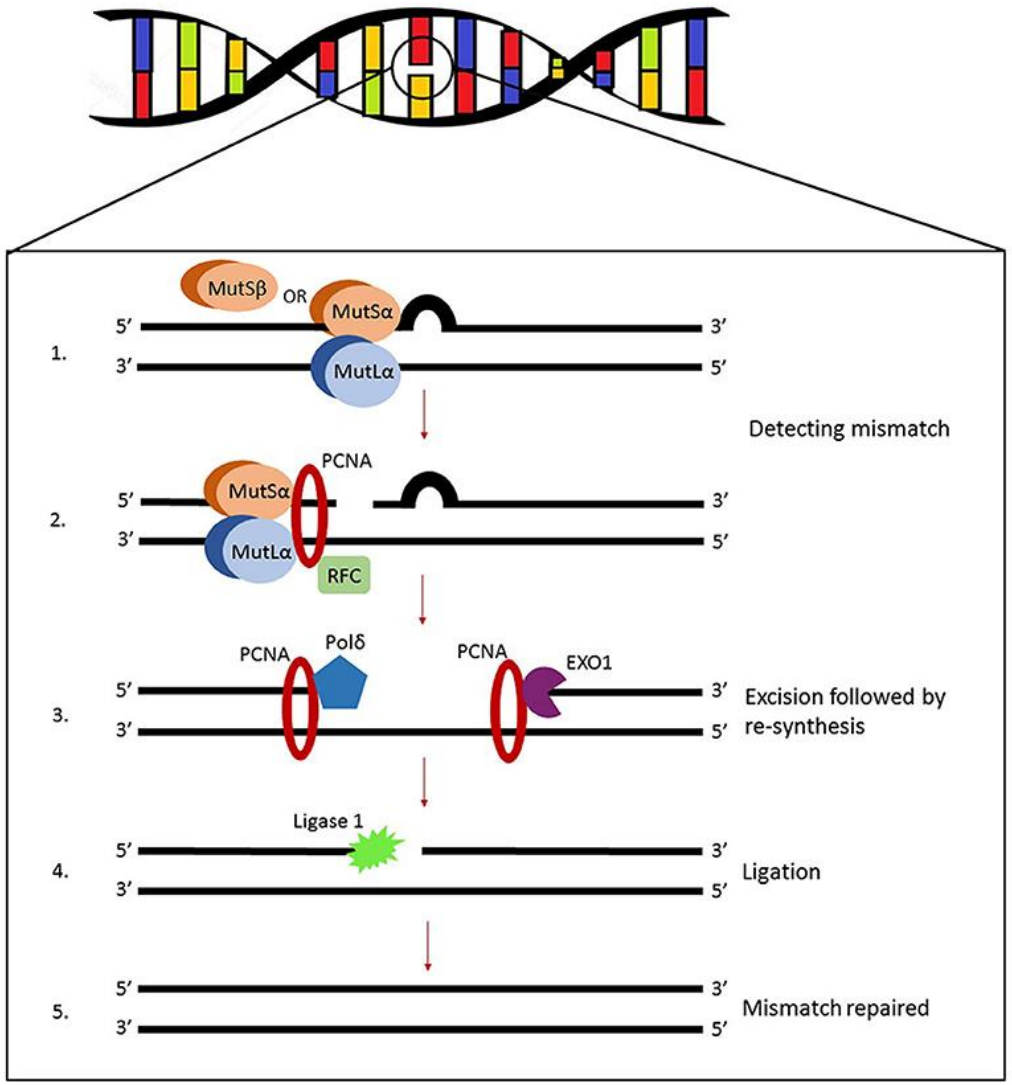
Mismatch repair

Recognition of a mismatch by the MSHs

Recruitment of the MLHs by ATP-bound MSHs that then connect the mismatch recognition signal to the distant DNA strand scission where excision begins

Excision of the DNA strand containing the wrong nucleotide

Resynthesis of the excision gap by the replicative DNA polymerase using the remaining DNA strand as a template (virtually identical to normal replicative DNA synthesis)



PMID: 32671096

Microsatellite Instability Testing

PCR

- Microsatellites are variable blocks of short repeating nucleotide sequences: 1-6 base pairs repeated 2-10 times – mostly in non-coding regions of the genome
- Prone to errors during DNA replication; DNA mismatch repair proteins normally recognize and repair these errors.
- Loss of function → high mutagenesis → high frequency of changes to length of microsatellites
- The National Cancer Institute microsatellite panel was optimized and correlated with IHC analysis in MMR-deficiency in colorectal cancer
  - 5 microsatellites tested: BAT25, BAT26, D5S346, D2S123, D17S250 (Mononucleotide Dinucleotide)
    - 1 unstable (<40%) = MSI-low or MSI-indeterminate
    - 2 or more unstable (≥40%) = MSI-high
- MSI is defined as a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumor when compared to normal tissue (this is limited by the analytical sensitivity of the assay)
- Dinucleotide repeats are less sensitive and specific than mononucleotide repeats for the identification of cancers with MMR deficiencies. A commercially available fluorescent multiplex assay that analyzes five nearly monomorphic mononucleotide microsatellite loci (*BAT-25*, *BAT-26*, *NR-21*, *NR-24*, and *MONO-27*) is available.

IHC

- Staining of MLH1, PMS2, MSH2, and MSH6 proteins
- Cheap, fairly easy to interpret
- Fixation issues

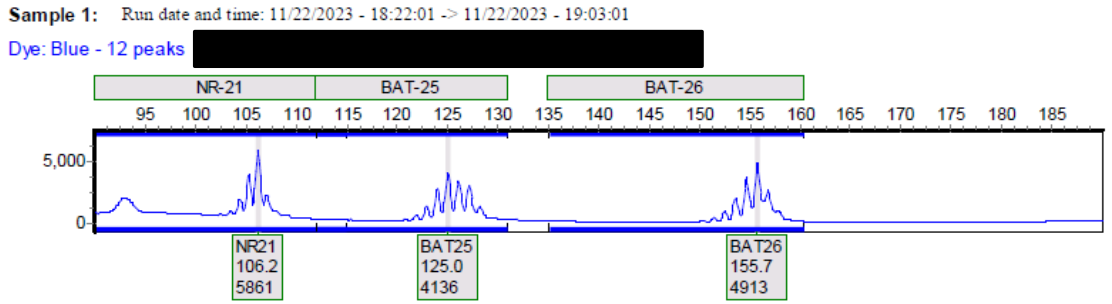
Sequencing

- Can integrate a number of microsatellites to determine MSI

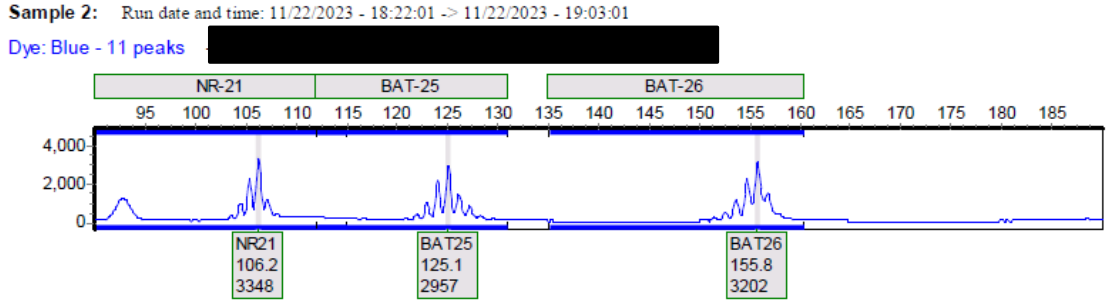
PMID: 9823339, 15528789

MSS

Normal tissue

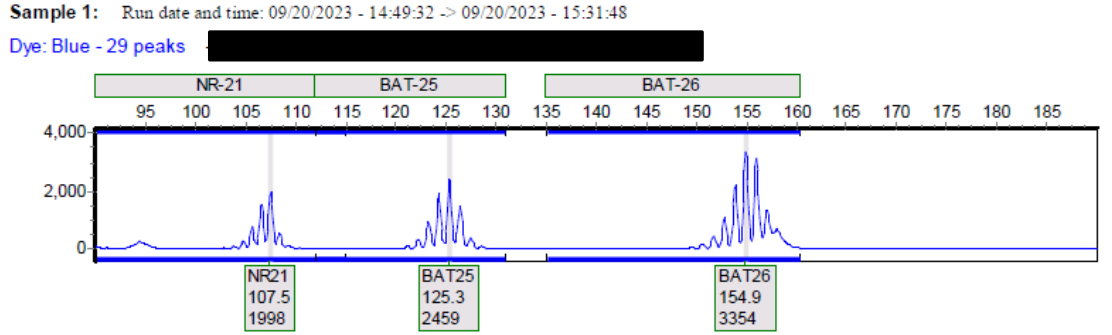


Tumor

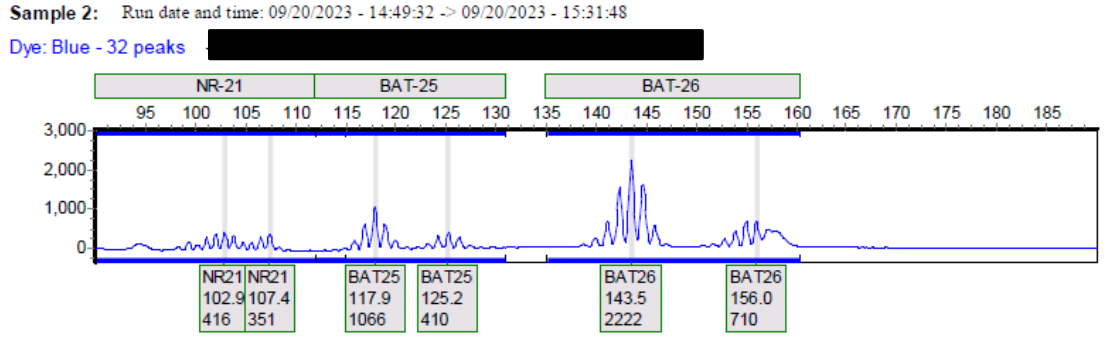


dMMR

Normal tissue



Tumor



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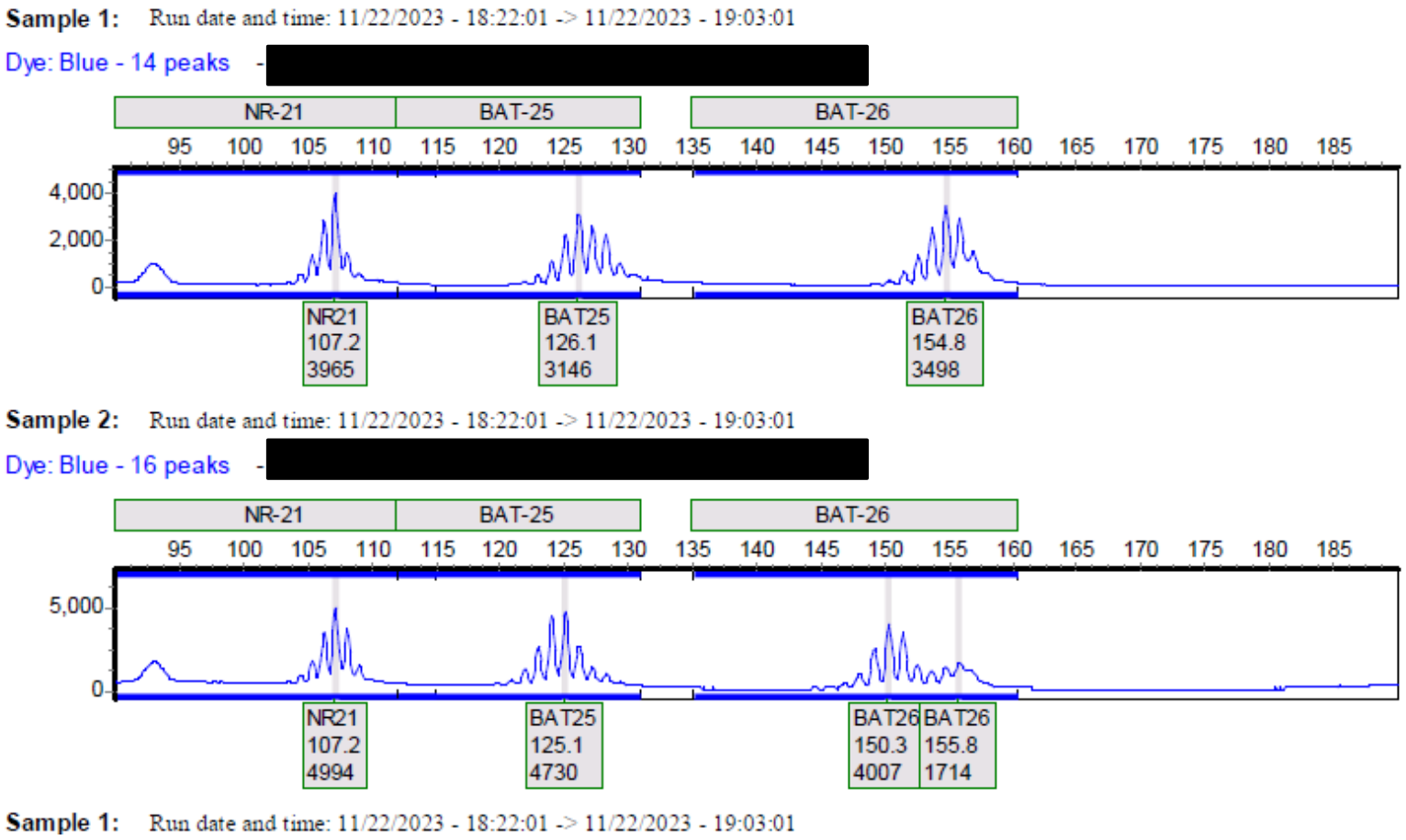
Endometrial cancers are much more likely to have 1-3 bp (minimal shifts)



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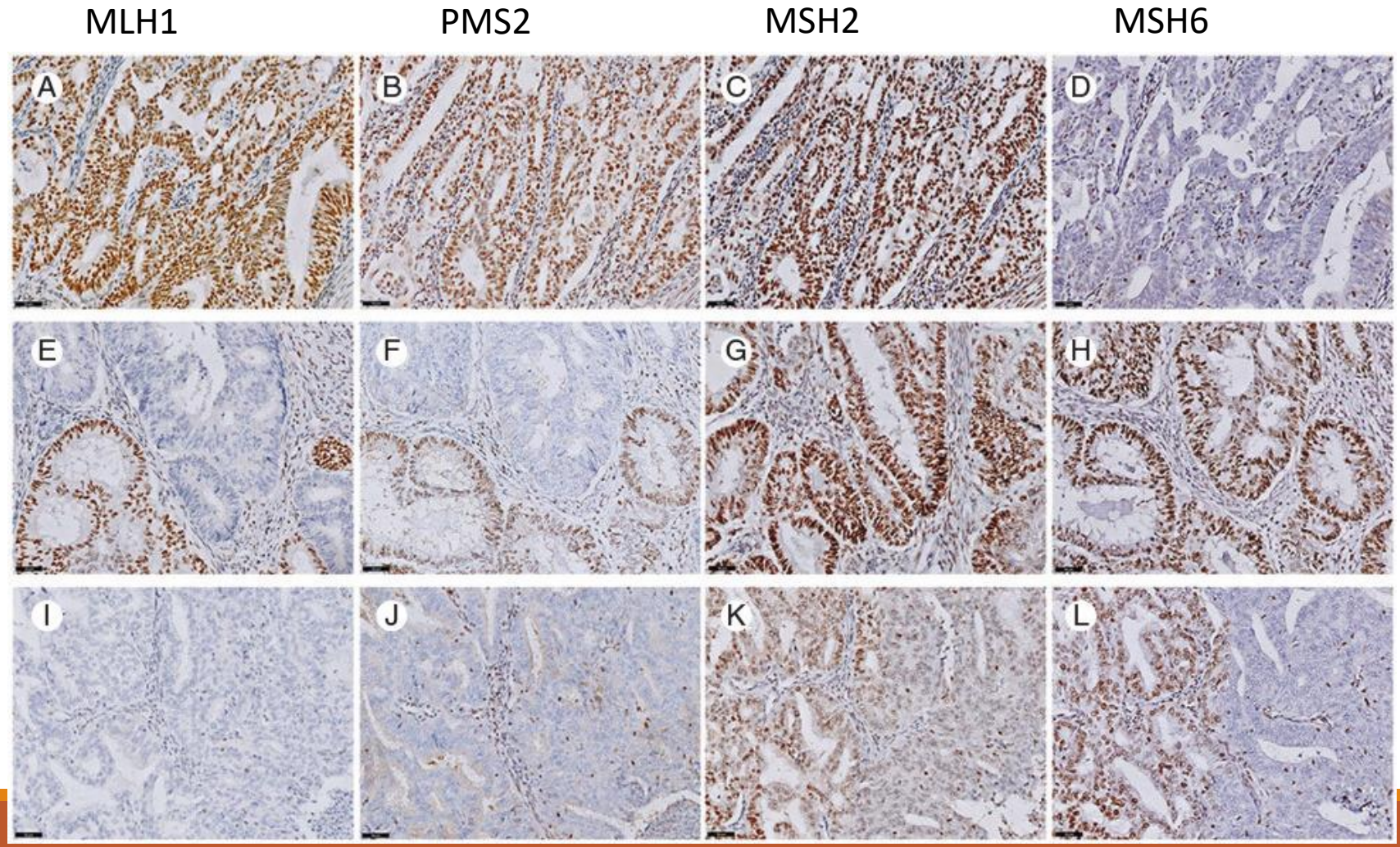
Immunohistochemistry



MSH6 protein loss

Subclonal loss of MLH1/PMS2

Complete loss of MLH1/PMS2

PMID: 27742654

MSI or MMR?

Table 1. Details on the MSI status and MMR protein expression in early-stage EC (n = 696)

MSI status	MMR protein expression					Count
	MLH1	PMS2	MSH6	MSH2	Protein expression	
MSS	1	1	1	1	Retained	496
MSS	2	2	1	1	Subclonal loss	6
MSS	1	1	2	2	Subclonal loss	2
MSS	0	0	1	1	Loss	8
MSS	1	1	0	1	Loss	3
MSS	1	1	0	0	Loss	1
MSI-L	1	1	1	1	Retained	1
MSI-L	2	2	1	1	Subclonal loss	2
MSI-L	0	0	1	1	Loss	4
MSI-L	1	0	1	1	Loss	2
MSI-L	1	1	0	1	Loss	2
MSI-H	1	1	1	1	Retained	2
MSI-H	2	2	1	1	Subclonal loss	8
MSI-H	0	0	2	1	Loss/subclonal loss	6
MSI-H	0	0	1	1	Loss	130
MSI-H	1	1	0	0	Loss	10
MSI-H	1	0	1	1	Loss	8
MSI-H	1	1	0	1	Loss	5

Mismatch repair protein expression was scored as following: 0—Complete loss; 1—Retained; 2—Subclonal loss. MMR—mismatch repair, MSS—microsatellite stable, MSI-L/H—microsatellite unstable with low or high frequency.

	Retained	Loss
MSS	496	20
MSI-L	1	10
MSI-H	2	167

Concordant in 655/696, kappa =0.854
Ambiguous cases (n = 41):
- subclonal loss (n=18)
- MSS with loss of MMR protein expression (n=20) [promoter methylation of MLH1 was identified in the majority of cases]
- MSI-L or MSI-H with retained MMR protein expression (n=3)

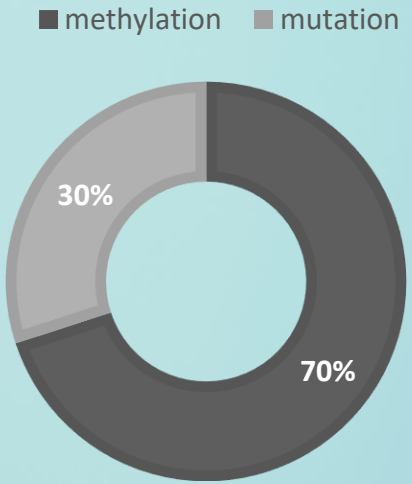
PMID: 27742654

dMMR – what's next?

MLH1 methylation

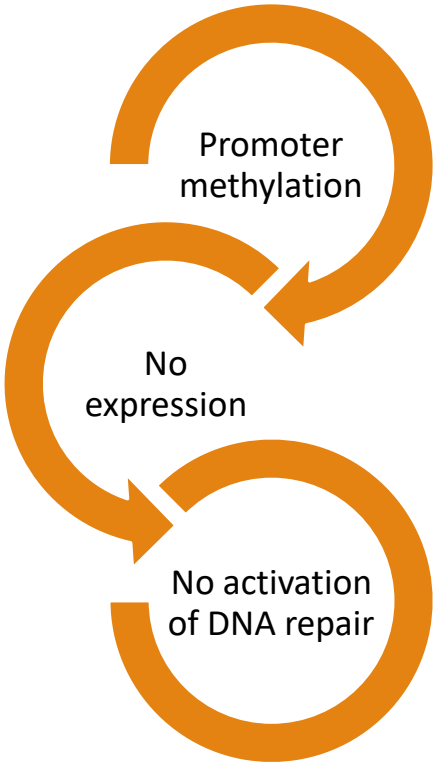
BRAF V600E

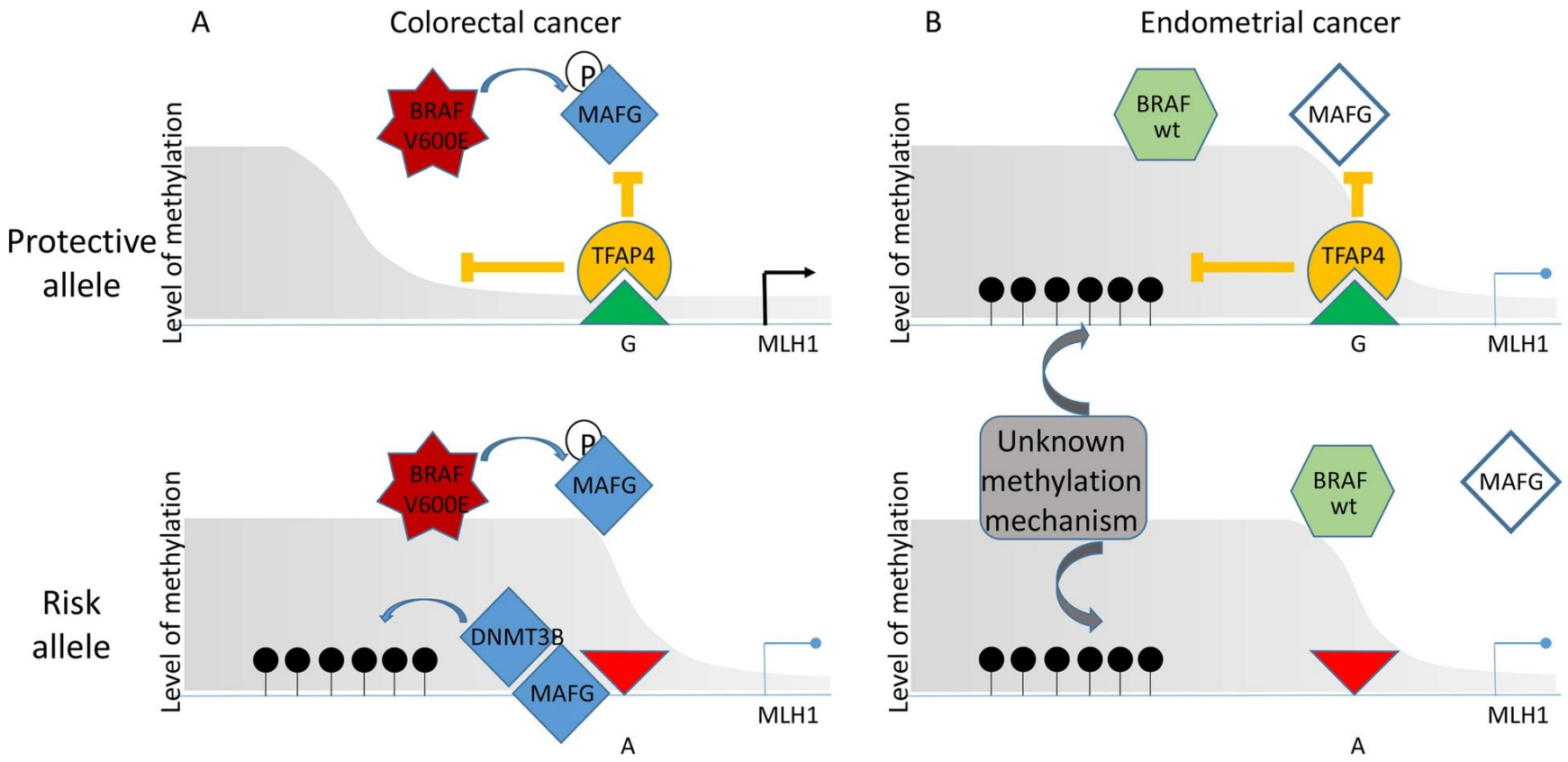
EPCAM deletion



PMID: 10072435

Loss of MLH1 is predominantly due to somatic silencing by promoter hypermethylation





PMID: 32641106

Subclonal dMMR

Subclonal loss of MMR protein expression generally corresponded to MLH1 promoter hypermethylation and subclonal MSI within microdissected area of the tumor.

MLH1+PMS2 subclonal loss → MLH1 promoter hypermethylation → sporadic intratumor heterogeneity

MSH6 +/- MSH2 subclonal loss→ unclear mechanism

MSH6 subclonal + MLH1/PMS2 complete loss → secondary MSI events in MSH6

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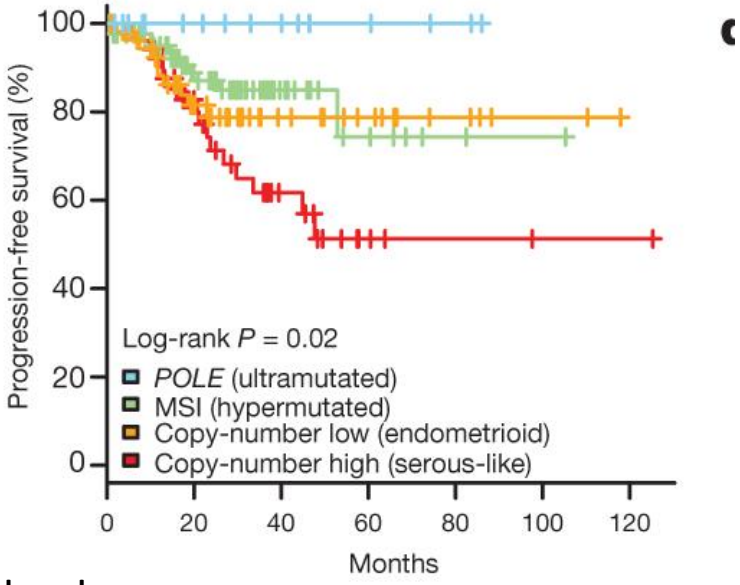
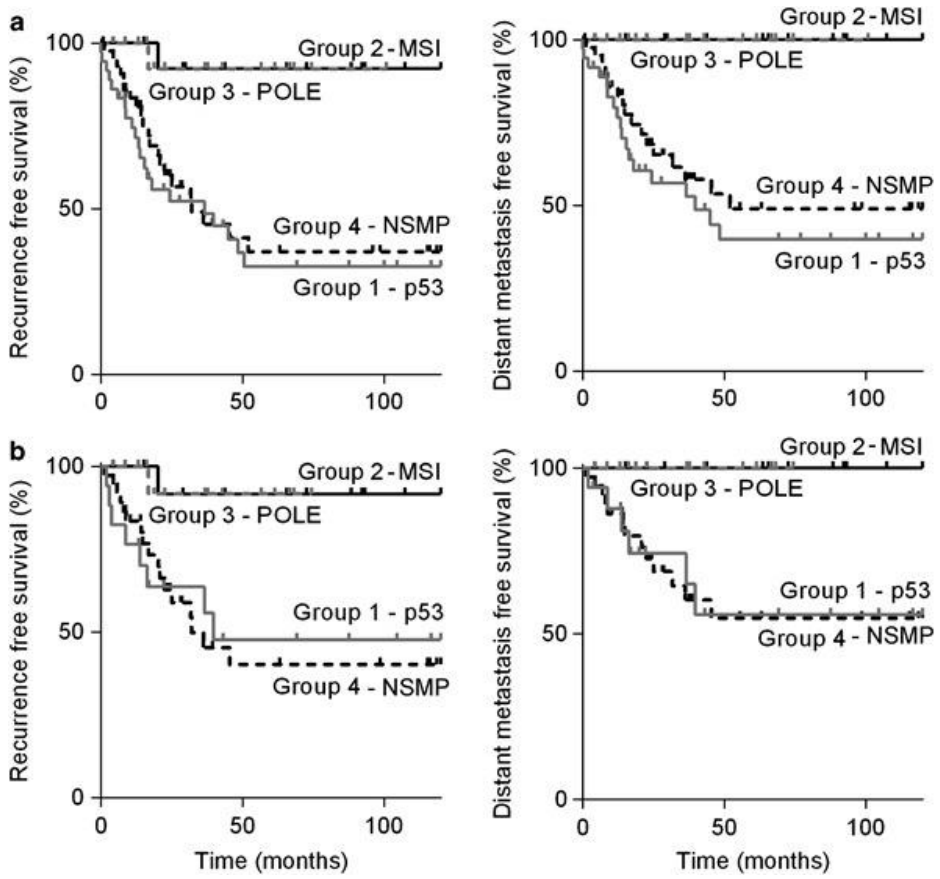
PMID: 27742654

Improved survival of MMRd and POLE mutants





High neoantigen loads
Increased tumor-infiltrating lymphocytes
Overexpression of PD-1 and PD-L1 in TILs and intraepithelial immune cells, but not tumor cells

Private Information

PMID: 23636398, 25720322, 26181000, 27159395

Check point inhibitors

Pembrolizumab: FDA-approved (in specific settings)

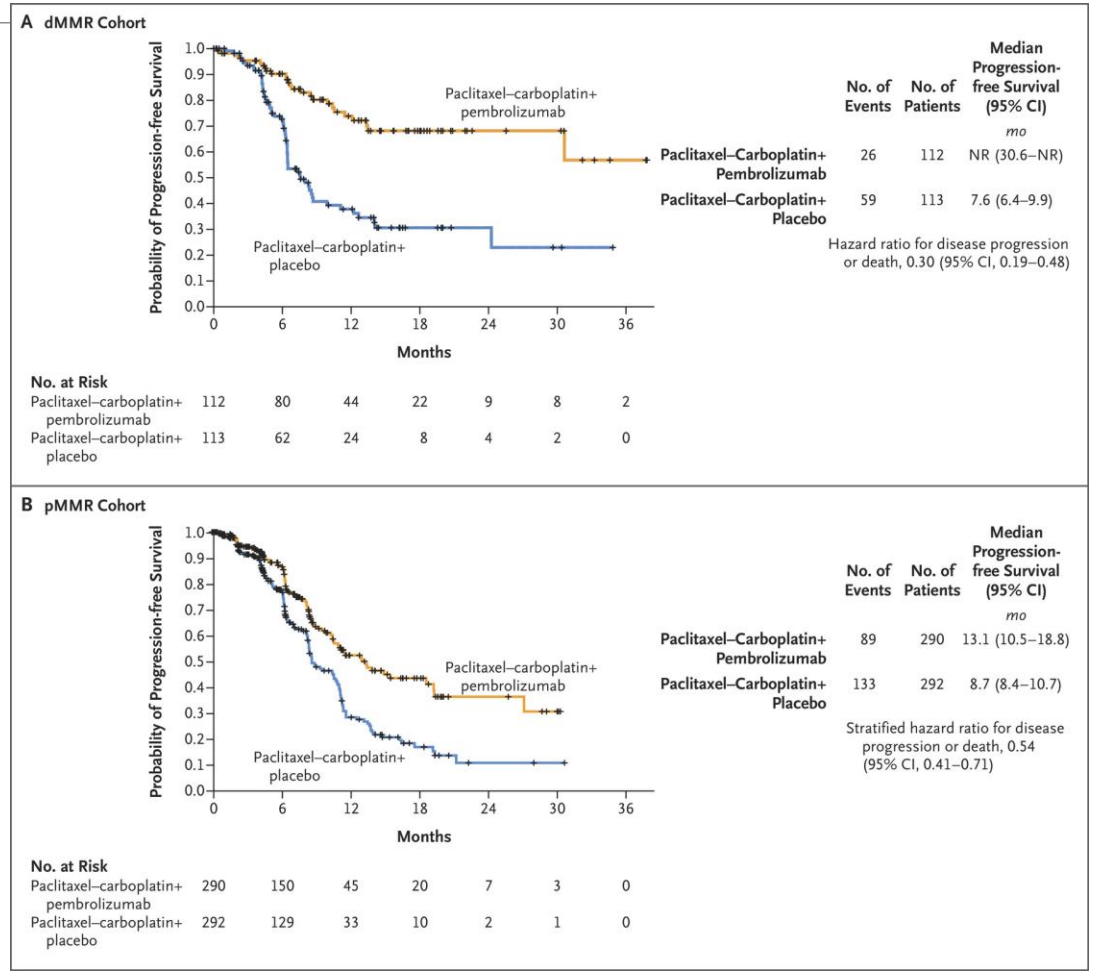
- dMMR as single agent (KEYNOTE-158)
- In combination with Lenvatinib for pMMR (KEYNOTE-775)

Dostarlimab: FDA-approved

- dMMR advanced solid tumors

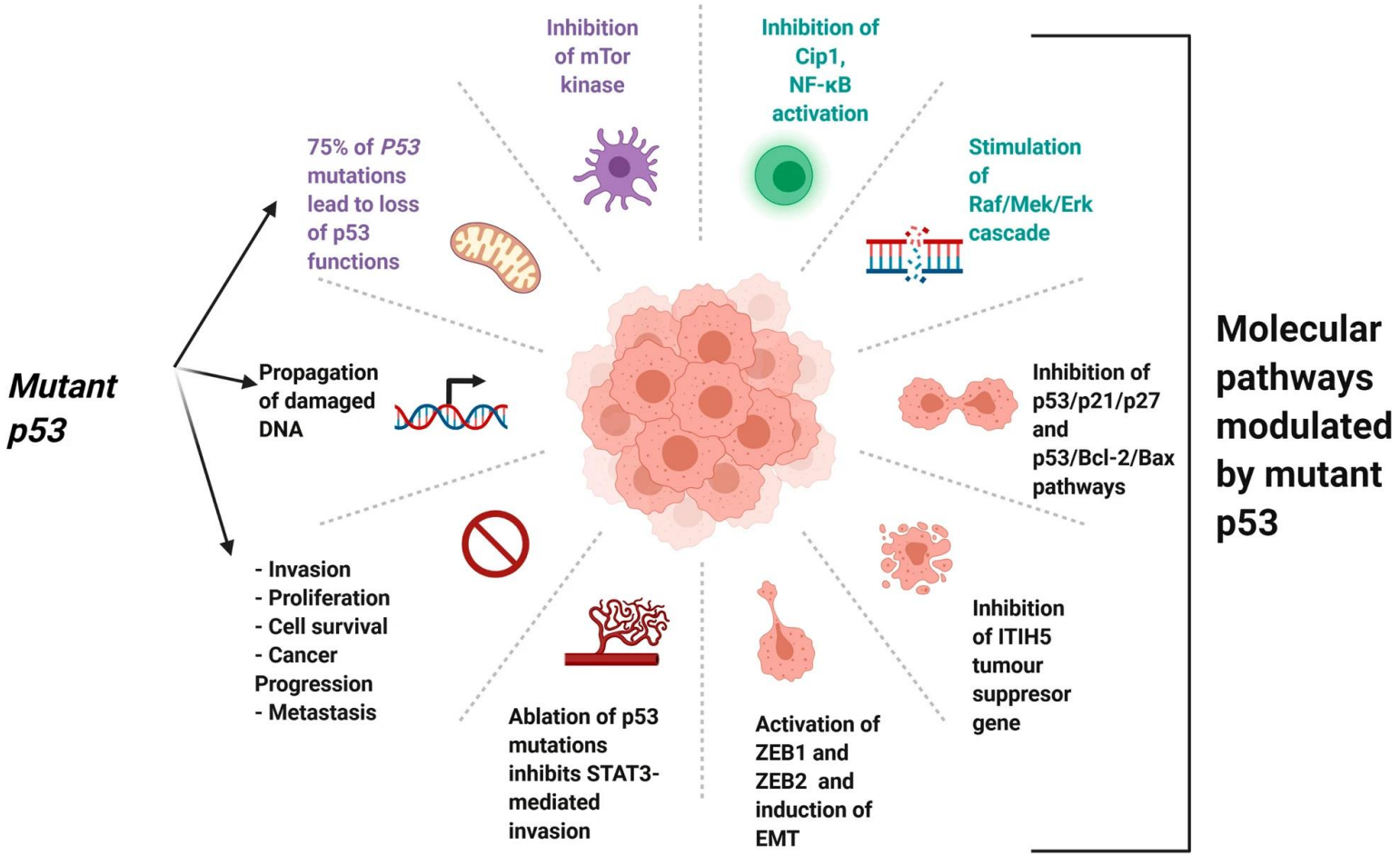
Recent advances in primary advanced or recurrent endometrial cancer including pMMR

- GY018: additional of Pembrolizumab
- RUBY: addition of Dostarlimab



PMID: 35680043, 36972022, 36972026

Private Information



Copy-number High

PMID: 34952583

Copy number high, low mutational burden

p53 IHC is a surrogate marker for this tumor group

Non-myoinvasive can present with extrauterine and metastatic disease

Primarily serous, but histologic type did not alter overall survival; stage being a better predictor

- Even grade 1 and 2 endometrioids can harbor TP53 mutations

Associated with HER2-positivity and homologous deficiency (HRD)

- ERBB2 amplification is most common (unfavorable clinical outcomes)
- May also harbor ERBB2 activating hotspot mutations point mutations which have shown association with sensitivity to anti-HER2 therapy in other cancer types

Private Information

PMID: 33602681

P53 IHC categories

Wild-type/normal: admixture of negative cells, weakly and strongly positive cells

Mutant overexpression: 80-100% of tumor cells show strong nuclear expression of p53. Commonly missense mutations in the DNA binding domain of TP53 resulting in nuclear accumulation of p53

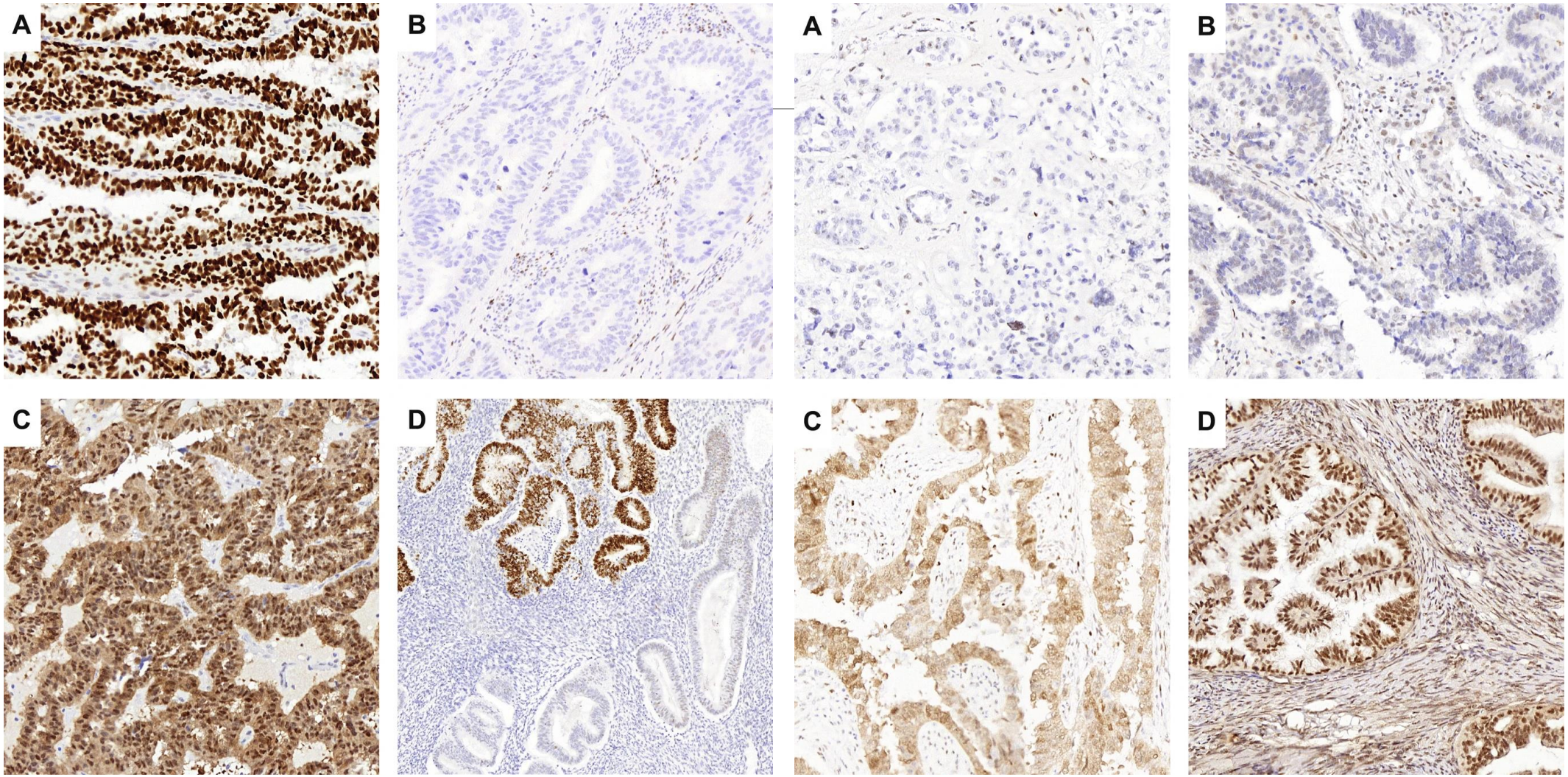
Null mutant pattern: loss of expression of p53 in all tumor cells, positive internal control must be present. Commonly frameshift or nonsense mutations

Cytoplasmic overexpression: unequivocal cytoplasmic staining accompanied by a variable nuclear staining. Commonly mutations in the tetramerization or C-terminal domain of TP53 (suggested >80% of the tumor)

Subclonal abnormal p53 expression: well-defined area within a tumor shows an abnormal p53 IHC pattern. *cutoffs for percent of tumor is unclear, studies have used 10% of tumor, <80% of tumor volume

Private Information

PMID: 29517499, 33290354



Private Information

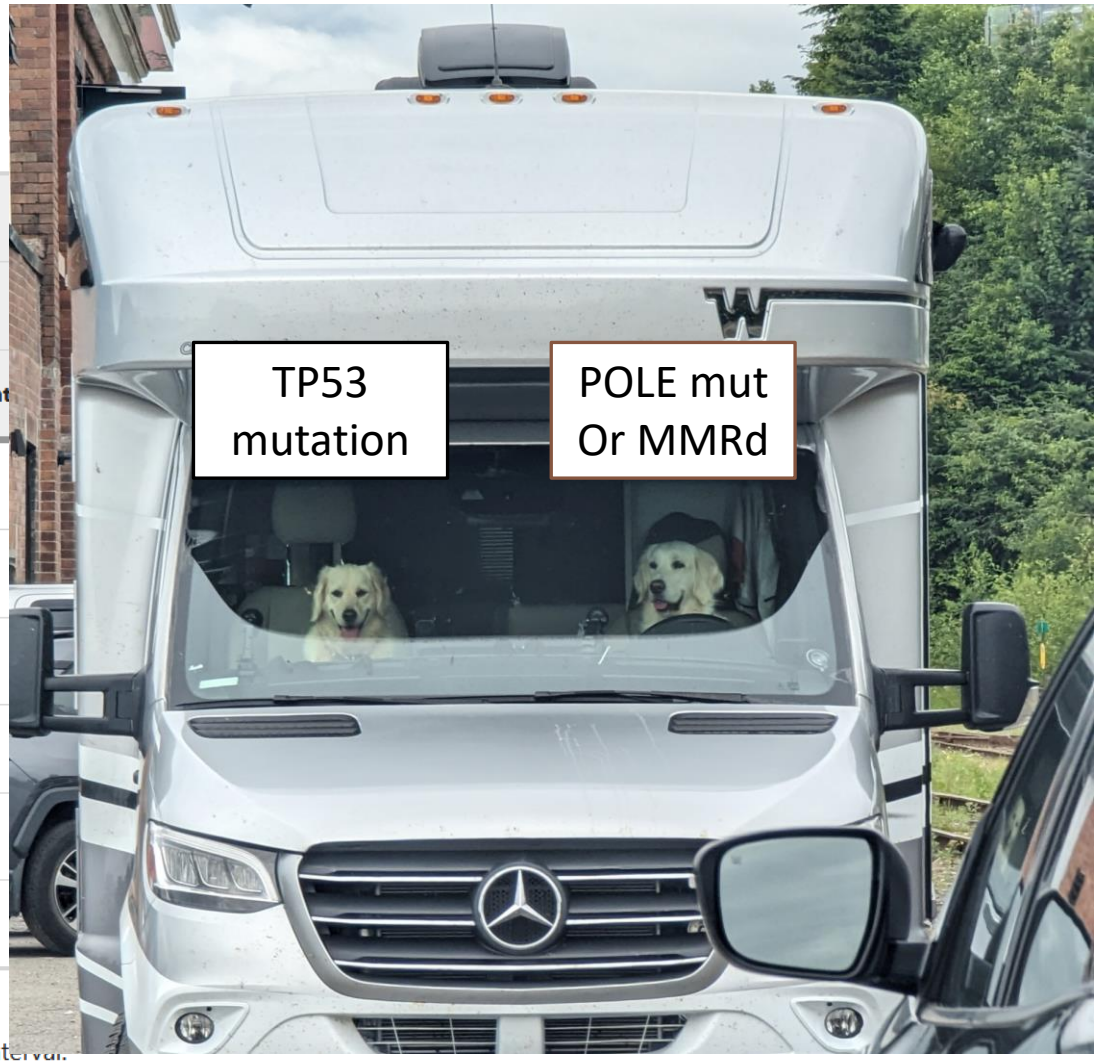
PMID: 35752743

P53 IHC vs Sequencing

	(Likely) pathogenic mutation on *TP53* NGS analysis			
	All EC		***POLE* wildtype and MMR proficient EC**	
p53 IHC	**Absent**	**Present**	**Absent**	**Present**
Wildtype	**215**	19	**96**	4
Abnormal	13	**97**	6	**76**
Total	228	116	102	80
Accuracy	90.7% (95% CI 87.6–93.8%)		94.5% (95% CI 89.4–99.6%)	
Sensitivity	83.6% (95% CI 79.7–87.5%)		95.0% (95% CI 90.2–99.8%)	
Specificity	94.3% (95% CI 91.8–96.7%)		94.1% (95% CI 88.9–99.3%)	

In bold, EC with concordant p53 IHC and sequencing for *TP53* mutations.

IHC immunohistochemistry, *NGS* next generation sequencing, *EC* endometrial cancer, *MMR* mismatch repair, *CI* confidence interval.



PMID: 35752743

HER2 Clinical trials

2010 – single agent trastuzumab failed to demonstrate therapeutic benefit

The addition of trastuzumab to carboplatin/paclitaxel increased PFS and OS in HER2+ uterine serosal cancer with the most benefit in stage III/IV disease. (NCT01367002)

NCCN: HER2 IHC testing with reflex to FISH is recommended for all serous and carcinosarcoma tumors. Consider HER2 testing for p53 abnormal carcinomas regardless of histology

Clear HER2 overexpression by IHC or FISH is associated with worse recurrence and survival outcomes in uterine serous carcinoma

Private Information

PMID: 19840887, 32709539, 32601075

HER2 scoring?

No current standard

The 2007 ASCO/CAP breast scoring system (>30% circumferential) yielded the highest concordance between IHC and FISH for HER2 expression in uterine serous carcinoma in one study

Table 1. Current criteria (approved or proposed) for HER2 positivity by IHC and FISH in different tumour types

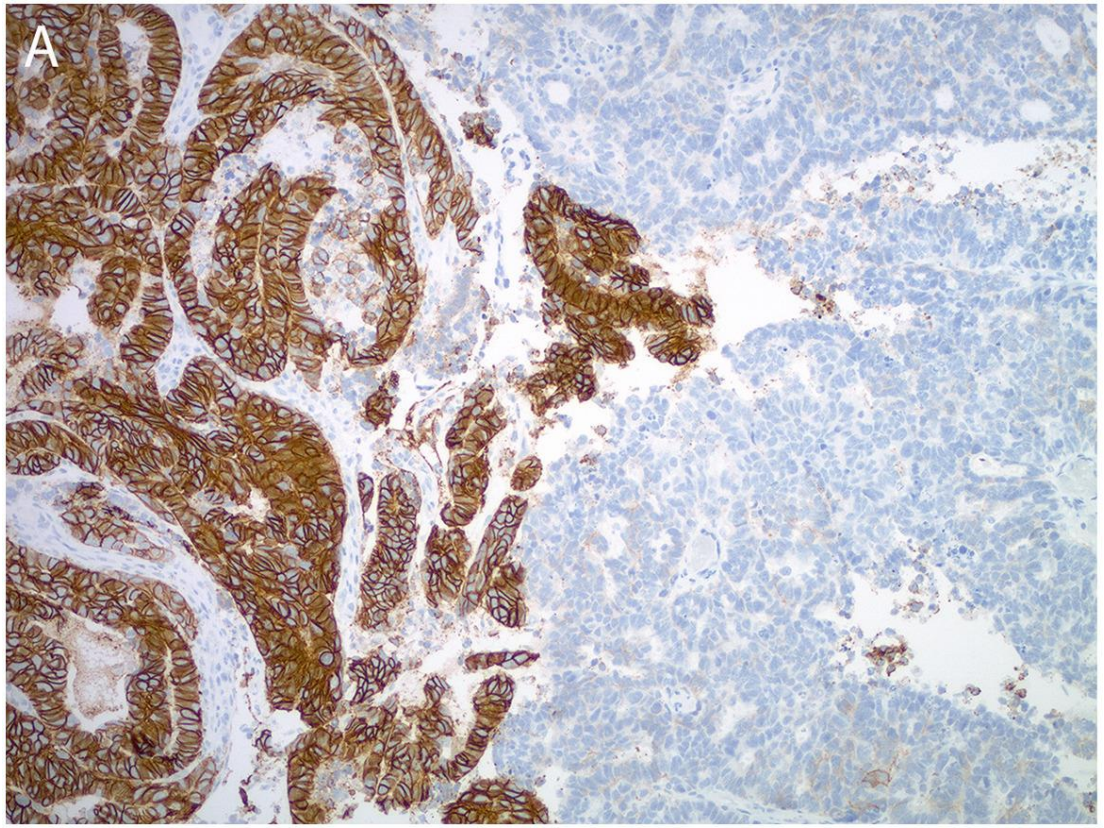
	HER2 IHC 3+	***HER2* FISH amplification**
Breast (ASCO/CAP 2018)	>10% circumferential, strong, complete	*HER2*/CEP17 ratio ≥2.0 and HER2 signal ≥4.0/nucleus OR ratio <2.0 and HER2 signal ≥6.0/nucleus (if IHC score 2+ or 3+)
Gastric/gastro-oesophageal junction (ASCO/CAP 2016)	≥10%, strong complete, or basolateral/lateral	*HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and HER2 signal >6.0/nucleus
Colorectal (HERACLES trial)	≥50% strong complete, or basolateral/lateral	*HER2*/CEP17 ratio ≥2.0 in ≥50% of cells

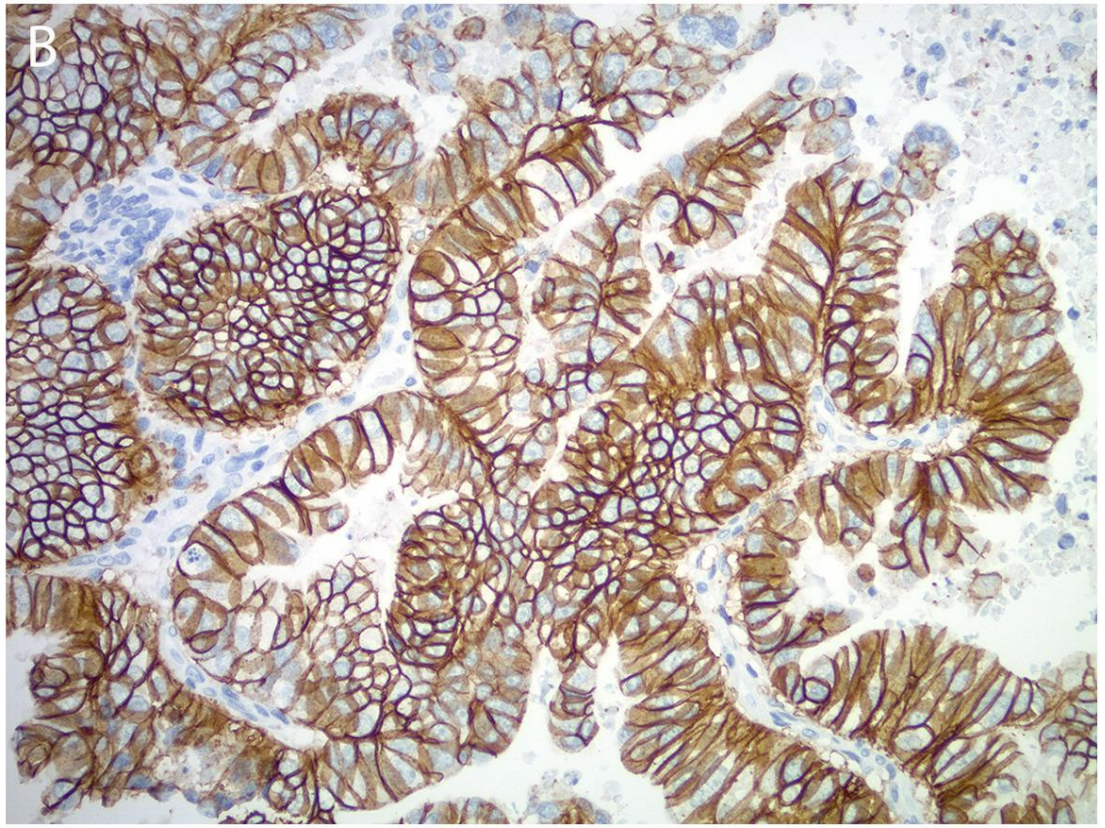
ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; FISH, fluorescent *in situ* hybridisation; IHC, immunohistochemistry.

Private Information

PMID: 36503635, 23765245

Lateral/basolateral membranous staining – still 3+





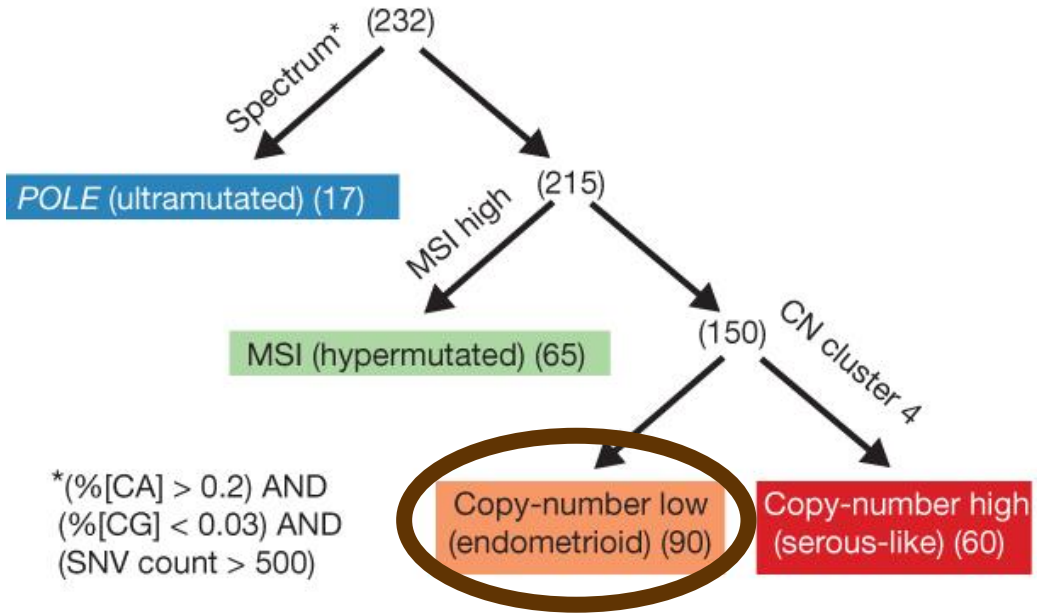
PMID: 36503635

No specific molecular profile (NSMP) / Low copy number

Prognosis between POLE-mutated and copy number-high

Heterogeneous group

In addition to hormonal therapy, maintenance therapy with selinexor (exportin-1 inhibitor) showed potential benefit in *p53*-wildtype cases in a subset analysis and is being investigated prospectively.



PMID: 37271639, 35365770

Mesonephric like endometrial cancer

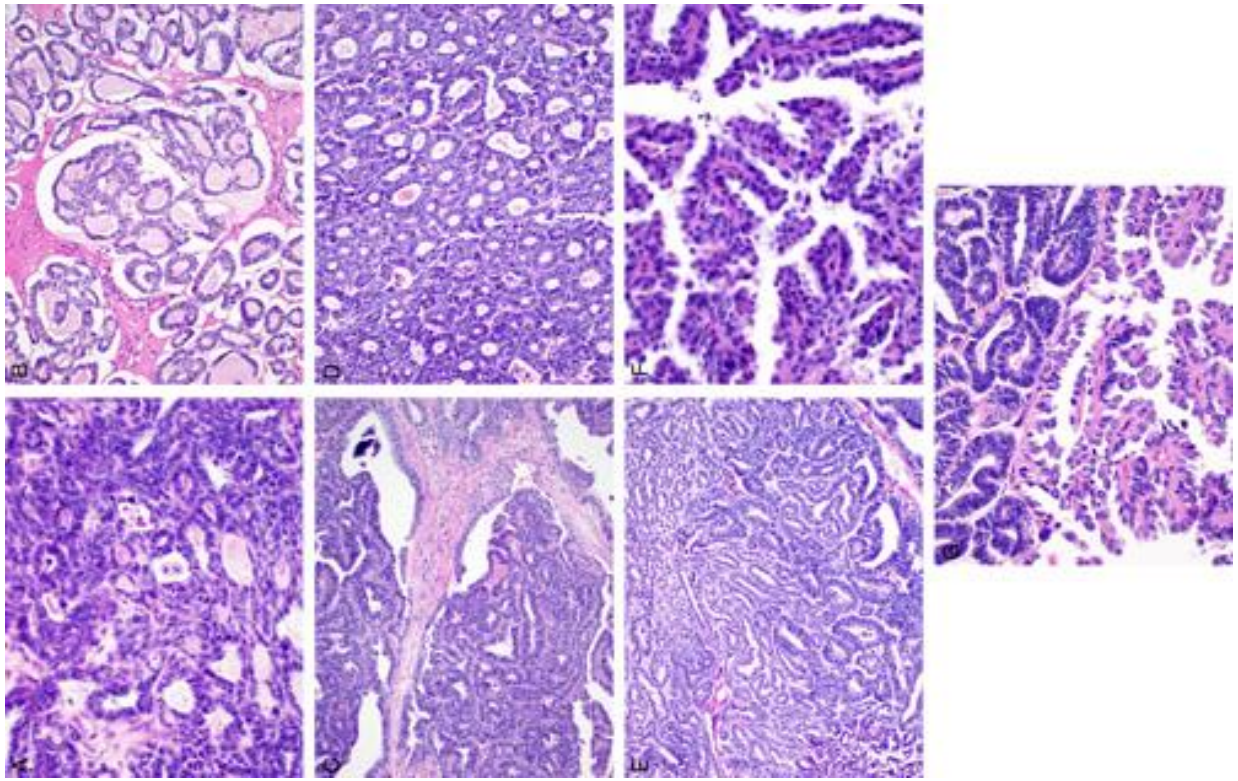
Rare and aggressive histotype

Current data suggest they are NSMP

- Appear to harbor KRAS mutations (p.G12 common), absent TP53, PTEN abnormalities

IHC:

- express TTF-1 and/or GATA3, PAX8 positive
- predominantly negative for hormone receptors including estrogen receptor (ER)
- pMMR



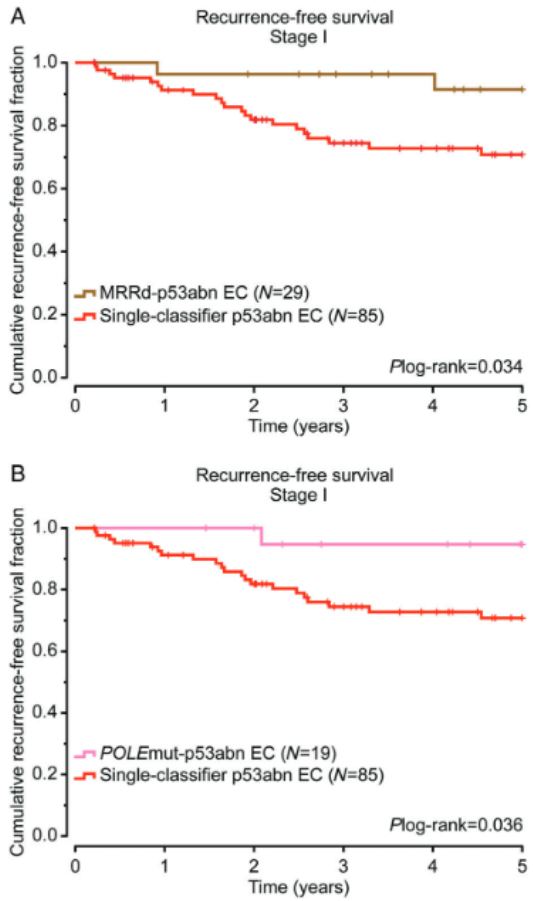
PMID: 28984674, 35195579, 37668797

More than one aberrancy?

3% (107/3353) of p53 abnormal had an additional aberrancy

- 64 MMRd-p53abn
- 31 POLEmut-p53abn
- 12 MMRd-POLEmut-p53abn

30 MSI-H + POLE EDM: 5yr recurrence-free survival comparable to previously reported POLE-ultramutated

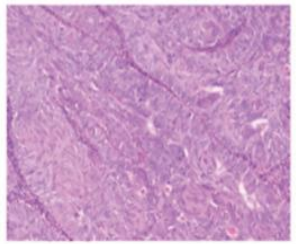


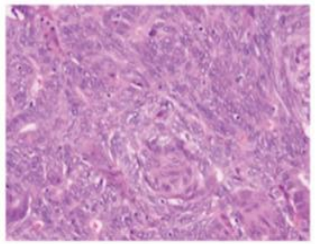
PMID: 31829447, 28795426

Private Information

	Use & utility			
	FDA approved EC biomarker	Predictive of response to agent	Prognostic	Exploratory
dMMR	✓	✓	✓	
MSI	✓	✓	✓	
TMB-H	✓	✓		
P53		✓	✓	✓
HER2		✓	✓	
ER/PR		✓	+/−	✓
L1CAM			✓	✓
CTNNB1			✓	✓
POLE			✓	✓
PD-L1			+/−	✓
ARID1A				✓
PI3K/AKT/mTOR				✓

PMID: 36399812

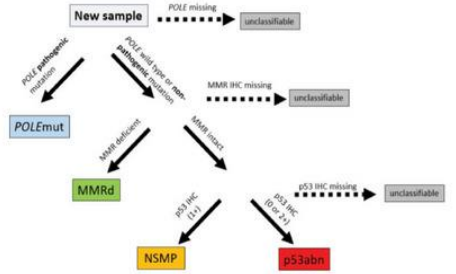




Endometrial Biopsy or Curettage

Pathology + Molecular Classification

Impact surgical decision /staging



*POLE*mut

Early ~90%

De-escalation e.g., surgery only

Advanced ~10%

? De-escalation
? Radiation only

Clinicopathologic and molecular parameters; e.g., LVI, grade, myoinvasion, L1CAM do not add prognostic or predictive stratification

Adjuvant Clincal Trials

PORTEC-4a (de-escalation)
RAINBO Blue (de-escalation)
TAPER (de-escalation)

MMRd

Adjuvant Radiation

? No additional benefit from chemotherapy

Loss of MSH6, MSH2, PMS2

Hereditary Cancer Referral

Consider ICB

Loss of MLH1

Not Methylated

Methylated

? Less response to ICB
? Pembro + Lenvat

Further stratified by MLH1 and immune profile?

Adjuvant Clincal Trials

NRG GY 020 (+ICB; pembrolizumab)
RAINBO Green (+ICB; durvalumab)
ADELE Trial (+ICB; tislelizumab)

NSMP

Additional Stratification

- LVI
- Grade
- ER/PR
- L1CAM?
- *CTNNB1?*
- Immune, e.g., CD8?

Highly Favourable

- De-escalation
- Vault brachy
- Endocrine therapy

Unfavourable

- ?Chemo RT
- ? Pembro + Lenvat

Clinicopathologic parameters do add prognostic and possible predictive stratification

Adjuvant Clincal Trials

RAINBO Orange (+endocrine therapy)
TAPER (de-escalation)

p53abn

Stage IA
No myoinvasion

- ?Surgery only
- ?Vault brachy
- ?ChemoRT

Stage IA with myoinvasion/Stage IB+

Significant benefit from chemotherapy

HRD (20-25%) PARPi

HER2 (20-25%) Anti-HER2 Rx

CCNE1 (20-30%) Wee1-i

Pembro + Lenvat (50% response in serous)

Aggressive tumors regardless of grade and histotype

Molecular parameters for predictive stratification

Adjuvant Clincal Trials

RAINBO Red (+PARPi; olaparib)
CAN-STAMP (+PARPi; niraparib)
NRG GY 026 (+HER2; trastuzumab/pertuzumab)

Private Information

PMID: 35657171

References 1

1. McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: Not your grandmother's cancer. Cancer. 2016 Sep 15;122(18):2787–2798. PMID: 27308732
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17–48. PMID: 36633525
3. Gilks CB, Oliva E, Soslow RA. Poor Interobserver Reproducibility in the Diagnosis of High-grade Endometrial Carcinoma. Am J Surg Pathol. 2013 Jun;37(6):874–881. PMID: 23629444
4. De Boer SM, Wortman BG, Bosse T, Powell ME, Singh N, Hollema H, Wilson G, Chowdhury MN, Mileshkin L, Pyman J, Katsaros D, Carinelli S, Fyles A, McLachlin CM, Haie-Meder C, Duvillard P, Nout RA, Verhoeven-Adema KW, Putter H, Creutzberg CL, Smit VTHBM. Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer. Ann Oncol. 2018 Feb;29(2):424–430. PMID: 29190319
5. The Cancer Genome Atlas Research Network, Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67–73. PMID: 23636398
6. Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, Van Der Steen-Banasik EM, Nijman HW, Putter H, Bosse T, Creutzberg CL, Smit VTHBM. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer—Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 2016 Aug 15;22(16):4215–4224. PMID: 27006490
7. León-Castillo A, De Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, Nijman HW, Singh N, Pollock PM, Bessette P, Fyles A, Haie-Meder C, Smit VTHBM, Edmondson RJ, Putter H, Kitchener HC, Crosbie EJ, De Bruyn M, Nout RA, Horeweg N, Creutzberg CL, Bosse T, on behalf of the TransPORTEC consortium. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020 Oct 10;38(29):3388–3397. PMID: 32749941
8. Wortman BG, Bosse T, Nout RA, Lutgens LCHW, Van Der Steen-Banasik EM, Westerveld H, Van Den Berg H, Slot A, De Winter KAJ, Verhoeven-Adema KW, Smit VTHBM, Creutzberg CL. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 2018 Oct;151(1):69–75. PMID: 30078506
9. van den Heerik ASVM, Horeweg N, Nout RA, Lutgens LCHW, van der Steen-Banasik EM, Westerveld GH, van den Berg HA, Slot A, Koppe FLA, Kommoss S, Mens JWM, Nowee ME, Bijmolt S, Cibula D, Stam TC, Jurgenliemk-Schulz IM, Snyers A, Hamann M, Zwanenburg AG, Coen VLMA, Vandecasteele K, Gillham C, Chargari C, Verhoeven-Adema KW, Putter H, van den Hout WB, Wortman BG, Nijman HW, Bosse T, Creutzberg CL. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer. 2020 Dec;30(12):2002–2007. PMID: 33046573
10. Magrin L, Fanale D, Brando C, Fiorino A, Corsini LR, Sciacchitano R, Filorizzo C, Dimino A, Russo A, Bazan V. POLE, POLD1, and NTHL1: the last but not the least hereditary cancer-predisposing genes. Oncogene. 2021 Oct 7;40(40):5893–5901. PMID: 34363023
11. Van Gool IC, Ubachs JEH, Stelloo E, de Kroon CD, Goeman JJ, Smit VTHBM, Creutzberg CL, Bosse T. Blinded histopathological characterisation of *POLE* exonuclease domain - mutant endometrial cancers: sheep in wolf's clothing. Histopathology. 2018 Jan;72(2):248–258. PMID: 28795426
12. Garmezy B, Gheeya J, Lin HY, Huang Y, Kim T, Jiang X, Thein KZ, Pilié PG, Zeineddine F, Wang W, Shaw KR, Rodon J, Shen JP, Yuan Y, Meric-Bernstam F, Chen K, Yap TA. Clinical and Molecular Characterization of *POLE* Mutations as Predictive Biomarkers of Response to Immune Checkpoint Inhibitors in Advanced Cancers. JCO Precis Oncol. 2022 May;(6):e2100267. PMID: 35108036
13. Kim G, Lee SK, Suh DH, Kim K, No JH, Kim YB, Kim H. Clinical evaluation of a droplet digital PCR assay for detecting *POLE* mutations and molecular classification of endometrial cancer. J Gynecol Oncol. 2022;33(2):e15. PMID: 34910396
14. León-Castillo A, Britton H, McConechy MK, McAlpine JN, Nout R, Kommoss S, Brucker SY, Carlson JW, Epstein E, Rau TT, Bosse T, Church DN, Gilks CB. Interpretation of somatic *POLE* mutations in endometrial carcinoma. J Pathol. 2020 Mar;250(3):323–335. PMID: 31829442
15. Casey L, Singh N. POLE, MMR, and MSI Testing in Endometrial Cancer: Proceedings of the ISGyP Companion Society Session at the USCAP 2020 Annual Meeting. Int J Gynecol Pathol. 2021 Jan;40(1):5–16. PMID: 33290350
16. Pećina-Šlaus N, Kafka A, Salamon I, Bukovac A. Mismatch Repair Pathway, Genome Stability and Cancer. Front Mol Biosci. 2020 Jun 26;7:122. PMID: 32671096
17. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for Cancer Detection and Familial Predisposition: Development of International Criteria for the Determination of Microsatellite Instability in Colorectal Cancer.
18. Bacher JW, Flanagan LA, Smalley RL, Nassif NA, Burgart LJ, Halberg RB, Megid WMA, Thibodeau SN. Development of a Fluorescent Multiplex Assay for Detection of MSI-High Tumors. Dis Markers. 2004;20(4–5):237–250. PMID: 15528789
19. Wu X, Snir O, Rottmann D, Wong S, Buza N, Hui P. Minimal microsatellite shift in microsatellite instability high endometrial cancer: a significant pitfall in diagnostic interpretation. Mod Pathol. 2019 May;32(5):650–658. PMID: 30443012
20. Stelloo E, Jansen AML, Osse EM, Nout RA, Creutzberg CL, Ruano D, Church DN, Morreau H, Smit VTHBM, Van Wezel T, Bosse T. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. Ann Oncol. 2017 Jan;28(1):96–102. PMID: 27742654
21. Simpkins SB, Bocker T, Swisher EM, Mutch DG, Gersell DJ, Kovatich AJ, Palazzo JP, Fishel R, Goodfellow PJ. MLH1 promoter methylation and gene silencing is the primary cause of microsatellite instability in sporadic endometrial cancers. Hum Mol Genet. 1999 Apr;8(4):661–666. PMID: 10072435
22. Russell H, Kedzierska K, Buchanan DD, Thomas R, Tham E, Mints M, Keränen A, Giles GG, Southey MC, Milne RL, Tomlinson I, Church D, Spurdle AB, O'Mara TA, Lewis A. The MLH1 polymorphism rs1800734 and risk of endometrial cancer with microsatellite instability. Clin Epigenetics. 2020 Dec;12(1):102. PMID: 32641106

Private Information

References 2

23. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, Leary A, Edmondson RJ, Powell ME, Crosbie EJ, Kitchener HC, Mileshkin L, Pollock PM, Smit VT, Creutzberg CL. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol. 2015 Jun;28(6):836–844. PMID: 25720322

24. Howitt BE, Shukla SA, Sholl LM, Ritterhouse LL, Watkins JC, Rodig S, Stover E, Strickland KC, D'Andrea AD, Wu CJ, Matulonis UA, Konstantinopoulos PA. Association of Polymerase e–Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol. 2015 Dec 1;1(9):1319. PMID: 26181000

25. Mehnert JM, Panda A, Zhong H, Hirshfield K, Damare S, Lane K, Sokol L, Stein MN, Rodriguez-Rodriquez L, Kaufman HL, Ali S, Ross JS, Pavlick DC, Bhanot G, White EP, DiPaola RS, Lovell A, Cheng J, Ganesan S. Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. J Clin Invest. 2016 May 9;126(6):2334–2340. PMID: 27159395

26. Maio M, Ascierto PA, Manzyuk L, Motola-Kuba D, Penel N, Cassier PA, Bariani GM, De Jesus Acosta A, Doi T, Longo F, Miller WH, Oh DY, Gottfried M, Xu L, Jin F, Norwood K, Marabelle A. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol. 2022 Sep;33(9):929–938. PMID: 35680043

27. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, Mannel R, Shahin MS, Cantuaria GH, Girda E, Mathews C, Kavecansky J, Leath CA, Gien LT, Hinchcliff EM, Lele SB, Landrum LM, Backes F, O'Cearbhaill RE, Al Baghdadi T, Hill EK, Thaker PH, John VS, Welch S, Fader AN, Powell MA, Aghajanian C. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2159–2170. PMID: 36972022

28. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, Gilbert L, Sharma S, Valabrega G, Landrum LM, Hanker LC, Stuckey A, Boere I, Gold MA, Auranen A, Pothuri B, Cibula D, McCourt C, Raspagliesi F, Shahin MS, Gill SE, Monk BJ, Buscema J, Herzog TJ, Copeland LJ, Tian M, He Z, Stevens S, Zografos E, Coleman RL, Powell MA. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145–2158. PMID: 36972026

29. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A, Cenciarelli C. p53 signaling in cancer progression and therapy. Cancer Cell Int. 2021 Dec;21(1):703. PMID: 34952583

30. Momeni-Boroujeni A, Dahoud W, Vanderbilt CM, Chiang S, Murali R, Rios-Doria EV, Alektiar KM, Aghajanian C, Abu-Rustum NR, Ladanyi M, Ellenson LH, Weigelt B, Soslow RA. Clinicopathologic and Genomic Analysis of *TP53* -Mutated Endometrial Carcinomas. Clin Cancer Res. 2021 May 1;27(9):2613–2623. PMID: 33602681

31. Köbel M, Ronnett BM, Singh N, Soslow RA, Gilks CB, McCluggage WG. Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility. Int J Gynecol Pathol. 2019 Jan;38(Supplement 1):S123–S131. PMID: 29517499

32. Köbel M, Kang EY. The Many Uses of p53 Immunohistochemistry in Gynecological Pathology: Proceedings of the ISGyP Companion Society Session at the 2020 USCAP Annual9 Meeting. Int J Gynecol Pathol. 2021 Jan;40(1):32–40. PMID: 33290354

33. Vermij L, Léon-Castillo A, Singh N, Powell ME, Edmondson RJ, Genestie C, Khaw P, Pyman J, McLachlin CM, Ghatage P, De Boer SM, Nijman HW, Smit VTHBM, Crosbie EJ, Leary A, Creutzberg CL, Horeweg N, Bosse T, Horeweg N, De Boer SM, Creutzberg CL, Bosse T, Smit VTHBM, Kroep J, Nout RA, Nijman HW, De Bruyn M, Powell ME, Singh N, Kitchener HC, Crosbie E, Edmondson R, Church DN, Leary A, Mileshkin L, Pollock PM, MacKay H. p53 immunohistochemistry in endometrial cancer: clinical and molecular correlates in the PORTEC-3 trial. Mod Pathol. 2022 Oct;35(10):1475–1483. PMID: 35752743

34. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, Chambers S, Secord AA, Havrilesky L, O'Malley DM, Backes FJ, Nevadunsky N, Edraki B, Pikaart D, Lowery W, ElSahwi K, Celano P, Bellone S, Azodi M, Litkouhi B, Ratner E, Silasi DA, Schwartz PE, Santin AD. Randomized Phase II Trial of Carboplatin–Paclitaxel Compared with Carboplatin–Paclitaxel–Trastuzumab in Advanced (Stage III–IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clin Cancer Res. 2020 Aug 1;26(15):3928–3935. PMID: 32601075

35. Erickson BK, Najjar O, Damast S, Blakaj A, Tymon-Rosario J, Shahi M, Santin A, Klein M, Dolan M, Cimino-Mathews A, Buza N, Ferriss JS, Stone RL, Khalifa M, Fader AN. Human epidermal growth factor 2 (HER2) in early stage uterine serous carcinoma: A multi-institutional cohort study. Gynecol Oncol. 2020 Oct;159(1):17–22. PMID: 32709539

36. Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM, Berek JS, Chapman JA, DiSilvestro PA, Horowitz IR, Fiorica JV. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol. 2010 Jan;116(1):15–20. PMID: 19840887

37. Talia KL, Banet N, Buza N. The role of HER2 as a therapeutic biomarker in gynaecological malignancy: potential for use beyond uterine serous carcinoma. Pathology (Phila). 2023 Feb;55(1):8–18. PMID: 36503635

38. Buza N, English DP, Santin AD, Hui P. Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. Mod Pathol. 2013 Dec;26(12):1605–1612. PMID: 23765245

39. Bogani G, Monk BJ, Coleman RL, Vergote I, Oakin A, Ray-Coquard I, Mariani A, Scambia G, Raspagliesi F, Bolognese B. Selinexor in patients with advanced and recurrent endometrial cancer. Curr Probl Cancer. 2023 Dec;47(6):100963. PMID: 37271639

40. Momeni-Boroujeni A, Nguyen B, Vanderbilt CM, Ladanyi M, Abu-Rustum NR, Aghajanian C, Ellenson LH, Weigelt B, Soslow RA. Genomic landscape of endometrial carcinomas of no specific molecular profile. Mod Pathol. 2022 Sep;35(9):1269–1278. PMID: 35365770

41. Brambs CE, Horn LC, Hiller R, Krücken I, Braun C, Christmann C, Monecke A, Höhn AK. Mesonephric-like adenocarcinoma of the female genital tract: possible role of KRAS-targeted treatment—detailed molecular analysis of a case series and review of the literature for targetable somatic KRAS-mutations. J Cancer Res Clin Oncol. 2023 Nov;149(17):15727–15736. PMID: 37668797

42. Mills AM, Jenkins TM, Howitt BE, Fan J, Ring KL, Cook I. Mesonephric-like Endometrial Carcinoma: Results From Immunohistochemical Screening of 300 Endometrial Carcinomas and Carcinosarcomas for This Often Overlooked and Potentially Aggressive Entity. Am J Surg Pathol. 2022 Jul;46(7):921–932. PMID: 35195579

43. Mirkovic J, McFarland M, Garcia E, Sholl LM, Lindeman N, MacConaill L, Dong F, Hirsch M, Nucci MR, Quick CM, Crum CP, McCluggage WG, Howitt BE. Targeted Genomic Profiling Reveals Recurrent KRAS Mutations in Mesonephric-like Adenocarcinomas of the Female Genital Tract. Am J Surg Pathol. 2018 Feb;42(2):227–233. PMID: 28984674

44. León-Castillo A, Gilvazquez E, Nout R, Smit VT, McAlpine JN, McConechy M, Kommoss S, Brucker SY, Carlson JW, Epstein E, Rau TT, Soslow RA, Ganesan R, Matias-Guiu X, Oliva E, Harrison BT, Church DN, Gilks CB, Bosse T. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. J Pathol. 2020 Mar;250(3):312–322. PMID: 31829447

45. Walsh CS, Hacker KE, Secord AA, DeLair DF, McCourt C, Urban R. Molecular testing for endometrial cancer: An SGO clinical practice statement. Gynecol Oncol. 2023 Jan;168:48–55. PMID: 36399812

46. Jamieson A, Barroilhet LM, McAlpine JN. Molecular classification in endometrial cancer: Opportunities for precision oncology in a changing landscape. Cancer. 2022 Aug;128(15):2853–2857. PMID: 35657171

Private Information

Slide by slide

Slide 3(McAlpine et al., 2016; Siegel et al., 2023)
Slide 4(De Boer et al., 2018; Gilks et al., 2013)
Slide 7(The Cancer Genome Atlas Research Network & Levine, 2013)
Slide 8(León-Castillo et al., 2020; Stelloo et al., 2016)
Slide 12(van den Heerik et al., 2020; Wortman et al., 2018)
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Slide 43(León-Castillo, Gilvazquez, et al., 2020; Van Gool et al., 2018)
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