Integrando la biología molecular en la anatomía patológica en tumores ginecológicos

Xavier Matias-Guiu, Hospital U Arnau de Vilanova, Hospital U de Bellvitge, Universities of Lleida and Barcelona, IRBLLEIDA, IDIBELL.

Disclosures

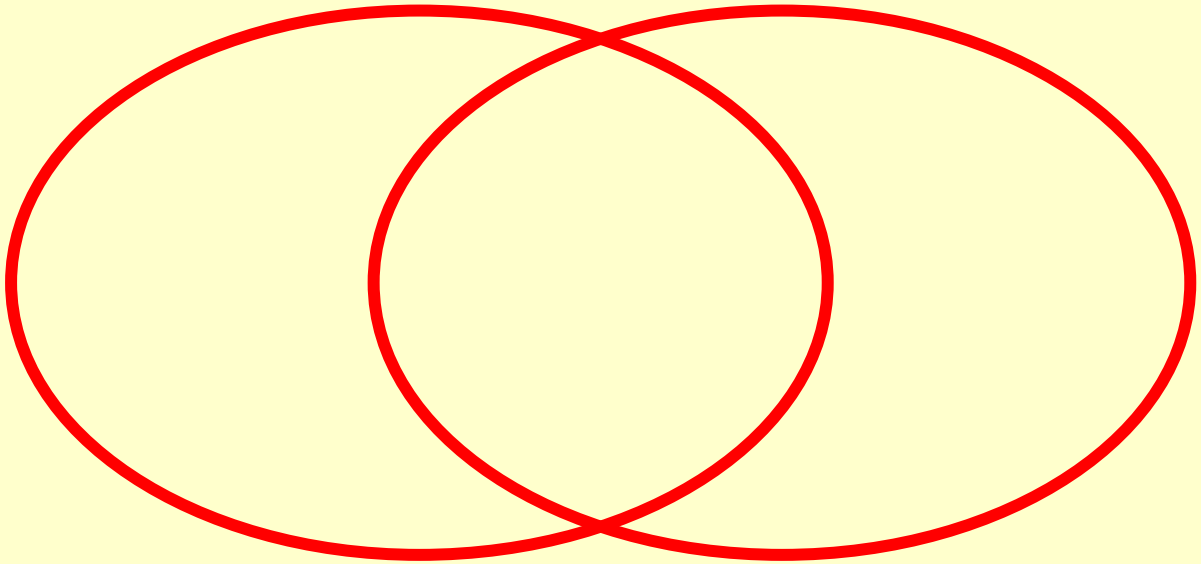
Lectures and associated travel expenses:

- Roche Farma, Qiagen, Ferrer Internacional, Novartis, Menarini, Biocartis, Agilent-Dako, Leyca, Reig Jofre, Sysmex, MSD, AstraZeneca, BMS, GSK, AstraZeneca

Advisory boards:

- AstraZeneca, Lilly, Amgen, GSK, Jansen, MSD, Illumina

Molecular Pathology



Morphology

Molecular Biology

Molecular Pathology:
Bringing genes to morphology

Ron DeLellis, 1991

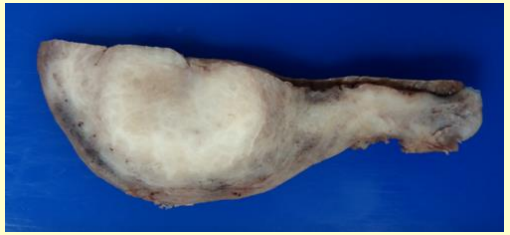
Morphology

Molecular Biology

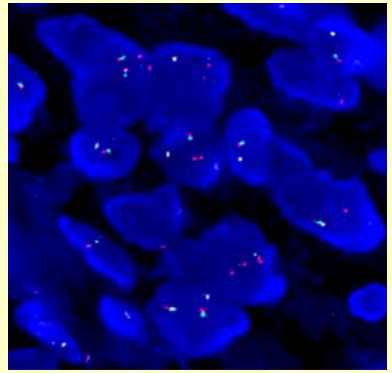
A two way trip

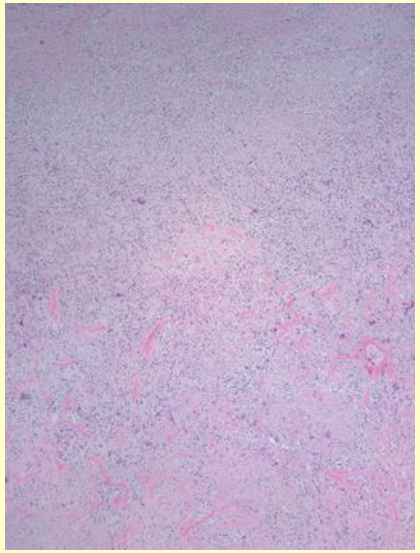
Molecular Pathology: The other way
From molecular profile to morphology

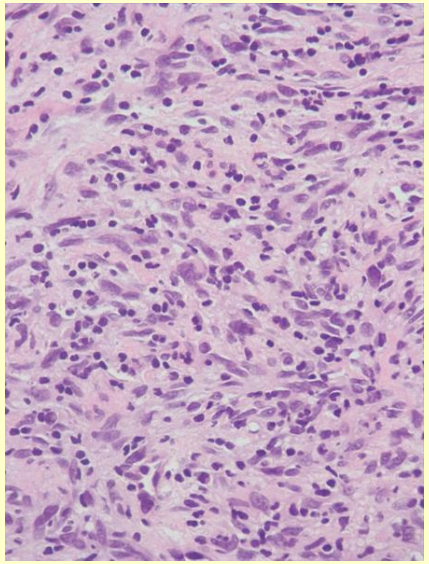
Endometrial Stromal Sarcomas, different molecular features; different morphology;

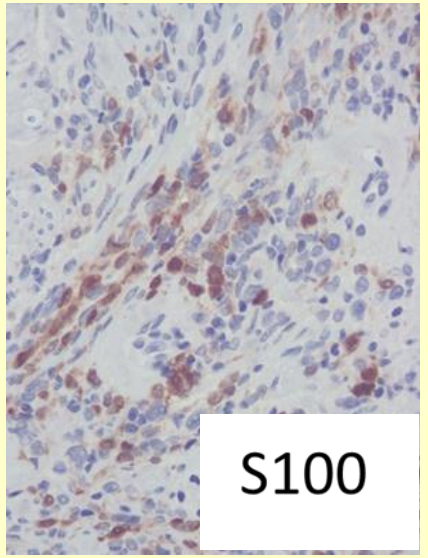


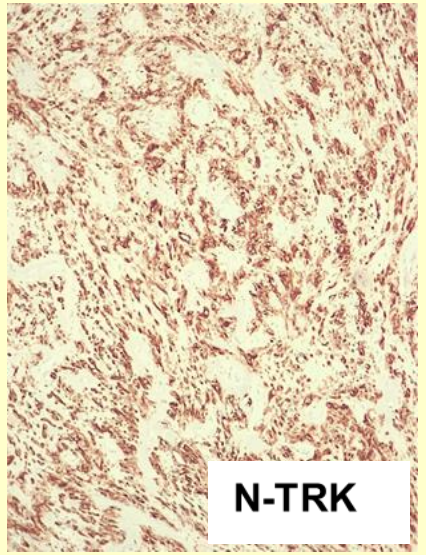
Region 5	Gene 5'	Exon 5'	Region 3	Gene 3'	Exon 3'	Split coverage	Mate split coverag	Total coverage	Quality
1:156104692	LMNA		1:156844290	NTRK1		24	23	47	High











Molecular Pathology, a 30 year journey; from research to diagnosis; The example of Uterine Sarcomas

WHO, 1994	WHO, 2021 and beyond
Low- grade endometrial stromal sarcoma	*Low- grade endometrial stromal sarcoma* • JAZF1, PHF1, MBTD1, EZHIP, EPC1 fusions
High- grade endometrial stromal sarcoma	*High- grade endometrial stromal sarcoma* • YWHAE-NUTM2A/B, BCOR fusions, BCOR ITD, • BCORL1 fusions, NOS *Undifferentiated endometrial sarcoma* *Other types* • Kinase fusions (NTRK, RET) • COL1-PDGFB • SMARCA4

Outline

1- Molecular risk stratification in ovarian cancer

2- Update on the molecular classification of endometrial cancer

3- Incorporation of molecular data into staging

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Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features

Jaime Prat

Virchows Arch

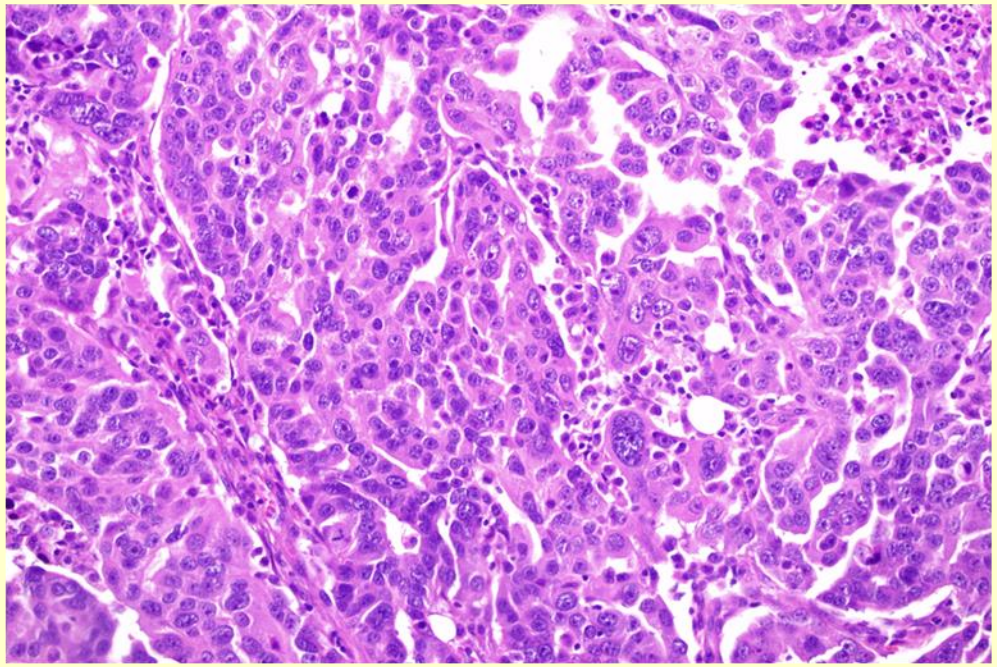
Table 1 Ovarian carcinoma: clinical and molecular features of the five most common types

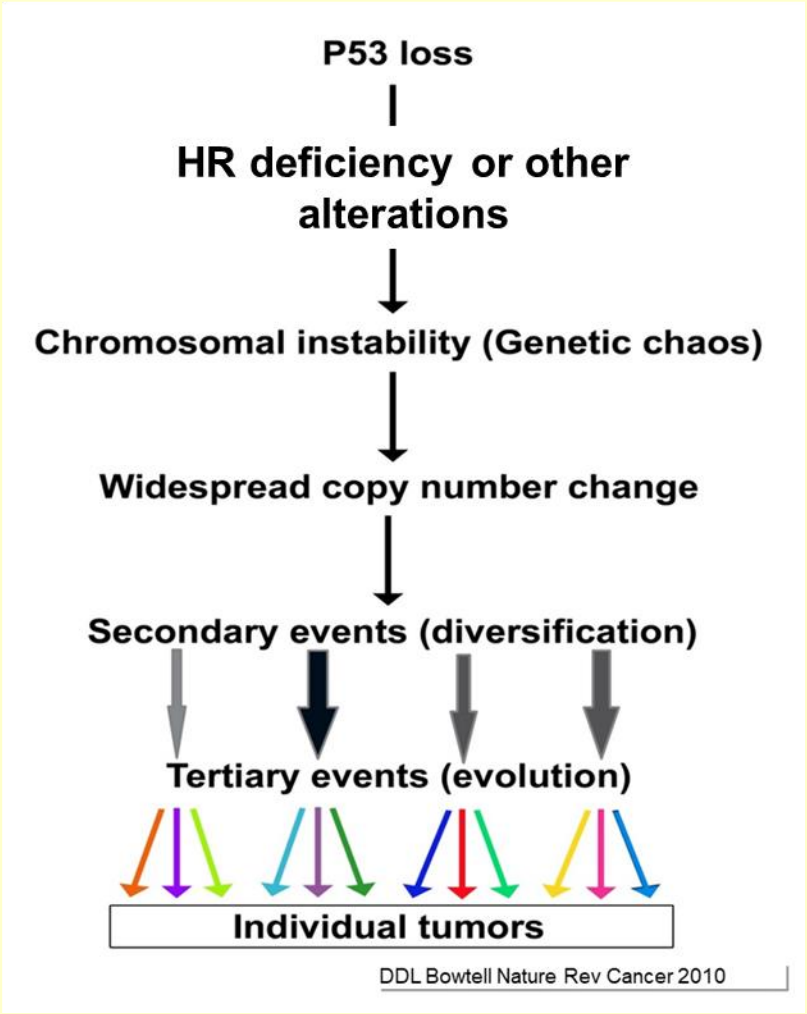
	HGSC	LGSC	MC	EC	CCC
Risk factors	*BRCA1/2*	?	?	HNPCC	?
Precursor lesions	Tubal intraepithelial carcinoma	Serous borderline tumor	cystadenoma/ borderline tumor?	Atypical endometriosis	Atypical endometriosis
Pattern of spread	Very early transcoelomic spread	Transcoelomic spread	Usually confined to ovary	Usually confined to pelvis	Usually confined to pelvis
Molecular abnormalities	*BRCA*, *p53*	*BRAF*, *KRAS*	*KRAS*, *HER2*	*PTEN ARID1A*	HNF1 *ARID1A*
Chemosensitivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

HGSC High-grade serous carcinoma, *LGSC* Low-grade serous carcinoma, *MC* Mucinous carcinoma, *EC* Endometrioid carcinoma, *CCC* Clear cell carcinoma, *HNPCC* Hereditary non-polyposis colorectal carcinoma

HGSC – Pathogenetic Model

High-grade serous carcinoma (G3)





Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

Here we report that high-grade serous ovarian cancer is characterized by *TP53* mutations in almost all tumours (96%)

International Journal of Gynecological Pathology
35:48–55, Lippincott Williams & Wilkins, Baltimore

Original Article

Molecular Alterations of *TP53* are a Defining Feature of Ovarian High-Grade Serous Carcinoma: A Rereview of Cases Lacking *TP53* Mutations in The Cancer Genome Atlas Ovarian Study

Russell Vang, M.D., Douglas A. Levine, M.D., Robert A. Soslow, M.D., Charles Zaloudek, M.D., Ie-Ming Shih, M.D., Ph.D., and Robert J. Kurman, M.D.

TABLE 1. *Rereview diagnoses and molecular data for TP53 wild-type high-grade serous carcinomas from the TCGA study*

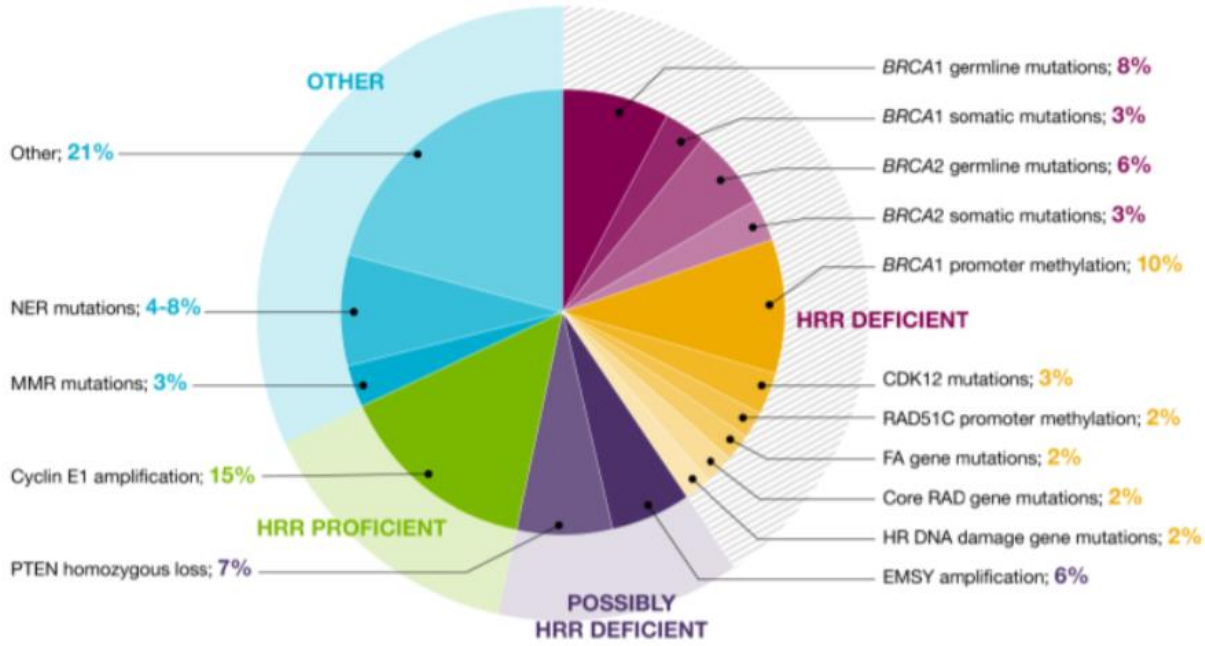
		Rereview pathologist					Molecular data from the TCGA(6)			
Case	TCGA*	*A*	*B*	*C*	*D*	*E*	*TP53* HD†	*BRCA*‡	No. Muts§	CNA (%)‖
1	09-2056	LGSC	HG Endo	LGSC	HGSC	HGSC	–	–	68	46
2	10-0933	Met	HG Endo	HG Endo	Met	Met	–	–	33	47
3	13-0727	HGSC¶	HGSC¶	HGSC¶	HGSC	HGSC	–	–	21	22
4	13-0755	CCC	LG/HGSC#	CCC	HGSC	HGSC	–	–	73	18
5	13-1408	HGSC	HGSC	HGSC	HGSC	HGSC	+	+	78	31
6	13-1477	LGSC	LGSC	LGSC	LGSC	LGSC	–	–	42	9
7	24-1544	Met	Met	Met	HGSC	HGSC	–	–	17	31
8	24-1565	HG Endo	HG Endo	HG Endo	HG Endo	HG Endo	–	–	25	9
9	24-2038	APST	APST	APST	APST	APST	–	–	10	11
10	25-1316	LGSC	HG Endo	LGSC	HGSC	HGSC	–	–	13	30
11	25-1328	LGSC	LGSC	LGSC	LGSC	LGSC	–	–	10	NA
12	25-2042	CCC	Adeno, NOS	HGSC	HGSC	HGSC	–	–	56	19
13	25-2408	LGSC	LGSC	LGSC	LGSC	LGSC	–	–	13	9
14	61-2095	LGSC	LGSC	LGSC	LGSC	LGSC	–	–	109	1

¶HGSC with LGSC architecture.

†Homozygous deletion of *TP53*.

Approximately half of high grade serous ovarian cancers harbour defects in homologous recombination[1]

BRCA mutations are the most common HRR pathway gene mutations in ovarian cancer



FA=Fanconi anemia; gBRCAm=Germline BRCA mutation; HRR=Homologous recombination repair; MMR=Mismatch repair; NER=Nucleotide excision repair; PTEN=Phosphatase and tensin homologue; sBRCAm=Somatic BRCA mutation

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

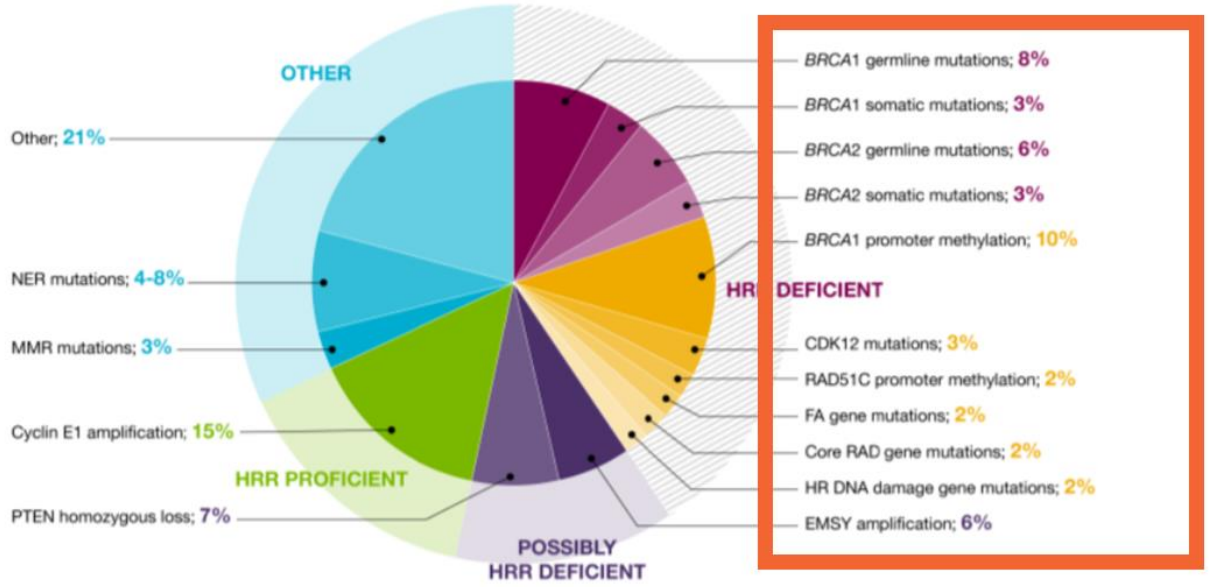
SPECIAL ARTICLE

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer

R. E. Miller[1,2], A. Leary[3], C. L. Scott[4,5], V. Serra[6], C. J. Lord[7,8], D. Bowtell[4,5], D. K. Chang[9,10], D. W. Garsed[4,5], J. Jonkers[11], J. A. Ledermann[12], S. Nik-Zainal[13,14], I. Ray-Coquard[15,16], S. P. Shah[17], X. Matias-Guiu[18], E. M. Swisher[19] & L. R. Yates[20,21*]

Approximately half of high grade serous ovarian cancers harbour defects in homologous recombination[1]

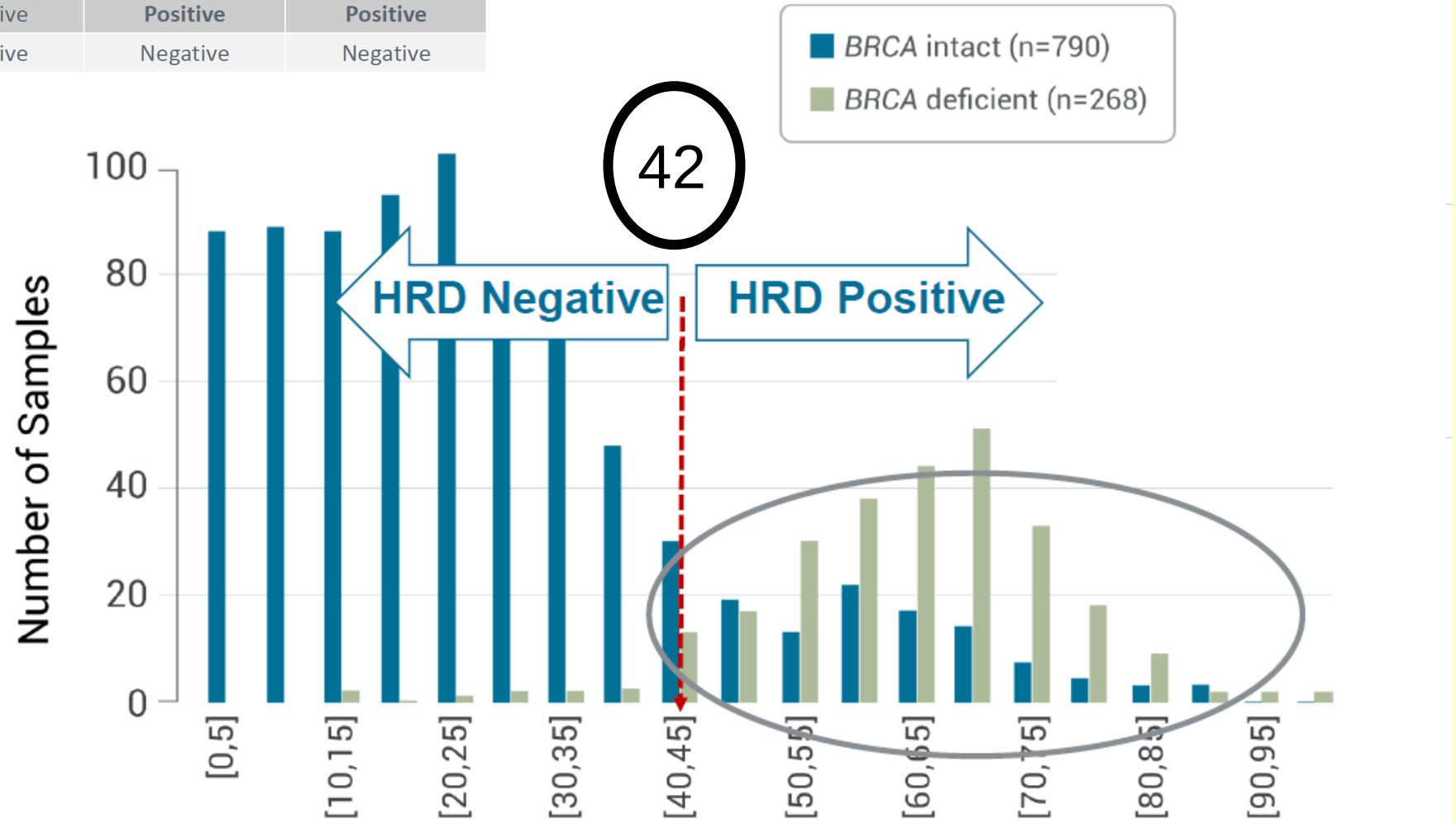
BRCA mutations are the most common HRR pathway gene mutations in ovarian cancer



FA=Fanconi anemia; gBRCAm=Germline BRCA mutation; HRR=Homologous recombination repair; MMR=Mismatch repair; NER=Nucleotide excision repair; PTEN=Phosphatase and tensin homologue; sBRCAm=Somatic BRCA mutation

Genomic scars

Genomic instability status	*tBRCA* status	Final Myriad HRD status
Positive	Negative	**Positive**
Positive	**Positive**	**Positive**
Negative	**Positive**	**Positive**
Negative	Negative	Negative



*BRCA deficient = tumor *BRCA1/2*-mutated or *BRCA1* promoter methylated

Timms et al. Br Ca Res (2014) 16:475-483
Hennessy et al. J Clin Oncol (2010) 28:3570-76
The Cancer Genome Atlas. Nature (2012) 490: 61-70
The Cancer Genome Atlas. Nature (2011) 474: 609-615

Ovarian Cancer Consensus Conference, Valencia June 20222

WORKING GROUP 1 RECOMMENDATIONS

Voting

Question 1

- What molecular and genomic tests should be performed at diagnosis as prognostic or predictive markers for tubo-ovarian carcinoma?

Recommendation 1.6

- A GI test that has been clinically validated in large cohorts [III, B] or preferably phase III trials should be used [I, A]

Consensus

- 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Percentages might not add up to 100% due to rounding. GI, genomic instability.

ESGO European Society of Gynaecological Oncology ESMO European Society of Pathology

Test	Origin	Type	Paola (Pts)	Failed
My choice	Myriad, USA	BRCAm + GIS	469	9
Leuven	Leuven Belgium	90000 SNPs + HRR panel	468	11
Geneva	HUG Switzerland	Normalized LST	469	2
NOGGO-GIS	Hamburg	20000 SNPs	383	4
Koln-NKI	Koln-NKI Germany-Netherlands	LOH scarring	469	
GIScar	Caen (France)	Instability score 127 genes	469	1
Curie	Curie-France	sWGS		
Sophia	France Switzerland	sWGS + gene panel	195	4
Illumina	Myriad/AZ/Illumina	Myriad assay	400	
SeqOne	France	sWGS + gene panel	400	
Heilderberg	Germany	AI	800	

Eric Pujade-Lauraine, Barcelona 2022

HRD in-house tests

Predictive value of the Leuven HRD test compared with Myriad myChoice PLUS

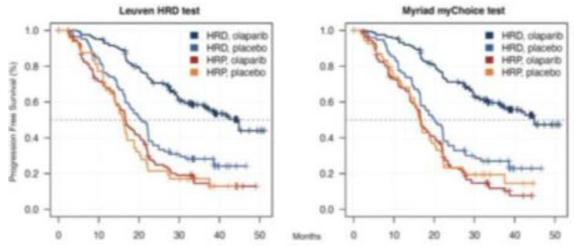
468 ovarian cancer samples from the PAOLA-1/ENGOT-ov25 trial.

Loveria L*, Vergote I*, Busschaert P, Vanderstichele A, Boecke B, Venken T, Harter P, Brems H, Van Nieuwenhuysen E, Pignata S, Baert T, Gonzalez-Martin A, Han S, Marth C, Neven P, Colombo N, Berteloot P, Mäenpää J, Olbrecht S, Luga T, Sablon E, Ray-Coquard I, Pujade Lauraine E, Lambrechts D**, Van Gorp T**

Agreement rates for Leuven HRD vs Myriad test

	Positive percent agreement	Negative percent agreement	Overall percent agreement
Overall HRD status	94%	86%	91%
BRCA analysis	95%	99.6%	98%
HRD GIS scoring	88%	86%	87%

HRD status versus PFS in PAOLA-1 (n=468)



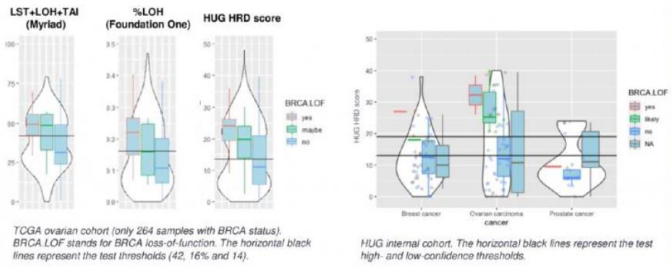
	Leuven HRD test	Myriad myChoice PLUS test
Definition of HR deficiency	Genomic instability score ≥ 56 and/or pathogenic BRCA mutation	Genomic instability score ≥ 42 and/or pathogenic BRCA mutation
Overall HRD status		
HRD status positive	254/468 (54%)	242/468 (52%)
HRD and BRCAm	147/468 (31%)	151/468 (32%)
HRD/only BRCAwt	107/468 (23%)	91/468 (19%)
HRP = HRD status negative	164/468 (35%)	182/468 (39%)
HRD status unknown	50/468 (11%)	44/468 (9%)
BRCA analysis		
Somatic BRCA mutation	147/468 (31%)	151/468 (32%)
BRCA wild type	320/468 (68%)	310/468 (66%)
Unknown	1/468 (0,2%)	7/468 (1,5%)
Other HRR gene mutations	4 RAD51C 1 RAD51D 2 BRIP1	Not reported in ENGOT HRD initiative subpopulation

HRD scoring with SNP assays

T. A. MCKEE[1], Y. CHRISTINAT[1], S. LEBOUBE[1], L. HO[1]
[1]Clinical Pathology Division, Geneva University Hospitals, Geneva, Switzerland

ACCURATE CLASSIFICATION OF BRCA-MUTATED SAMPLES AS HRD-POSITIVE

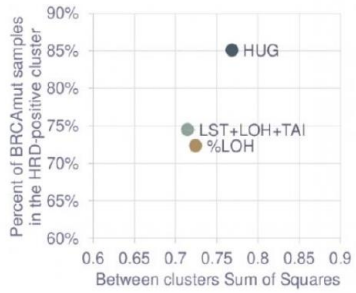
Optimized on the TCGA HGSOC cohort and validated on an internal cohort of HUG patients who received a CNV analysis as part of their clinical itinerary (47 breast ductal carcinomas, 51 ovarian carcinomas and 16 prostate carcinomas)



TCGA ovarian cohort (only 264 samples with BRCA status). BRCA LOF stands for BRCA loss-of-function. The horizontal black lines represent the test thresholds (42, 16% and 14).

HUG internal cohort. The horizontal black lines represent the test high- and low-confidence thresholds.

BETTER SEPARATION OF SAMPLES INTO TWO DISTINCT CLUSTERS



Y-axis: Percentage of samples with a BRCA loss-of-function classified as HRD-positive (264 HGSOC; TCGA)

X-axis: Measure of distance (with respect to the test metrics) between the samples classified as HRD positive and negative. A large value is indicative of a good separation (457 HGSOC and 112 TNBC; TCGA)

Clinical relevance evaluation of a novel homologous recombination deficiency CE-IVD decentralized solution

A. Buisson[*1], P. Saintigny[1], A. Harlé[2], D. Vacirca[3], M. Barberis[3], P. Gilson[2], C. Roma[4], F. Bergantino[4], C. Grimm[5], L. Müllauer[6], P. Harter[7], S. Pignata[8], A. Gonzalez-Martin[9], C. Schauer[10], K. Fujiwara[11], I. Vergote[12], N. Colo

1 Highlights

- The novel **deep learning-based, decentralized SOPHiA DDM™ Dx HRD Solution (SOPHiA GENETICS SA)** determines homologous recombination deficiency (HRD) status in ovarian cancer samples.
- The PFS clinical relevance* metric was **non-inferior** when HRD status was determined with the SOPHiA DDM™ Dx HRD Solution compared to Myriad myChoice® CDx.
- The SOPHiA DDM™ Dx HRD Solution **was highly concordant (overall percentage of agreement** [OPA] = **93.03%)** with the reference method, Myriad myChoice® CDx.
- This multicenter validation study demonstrates the **clinical utility of the CE-IVD-certified, decentralized SOPHiA DDM™ Dx HRD Solution** for the accurate identification of HRD-positive ovarian cancer patients that could potentially benefit from first-line maintenance treatment with PARP inhibitors (Clinical Decision Support Only).

Sample	Processed across 4 independent laboratories	Processed at SOPHiA GENETICS laboratory	Total
Analytical performance study			
Overall	84	235	**318**
Myriad GI status available	77	210	287[a]
Myriad GI score available	75	41	116[a]
Clinical relevance* study			
PAOLA-1 clinical trial	NA	195	**195[a]**

Table 1. Details of samples used to test the analytical and clinical relevance* of SOPHiA DDM™ Dx HRD Solution.
* Samples had GI conclusive results with both assays. GI, genomic instability; Myriad, Myriad MyChoice® CDx.

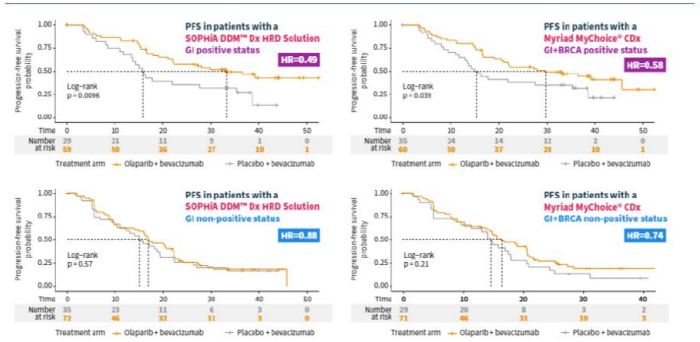


Figure 2. Progression-free survival in a PAOLA-1 sub-cohort of patients stratified according to SOPHiA DDM™ Dx HRD Solution GI status or Myriad MyChoice® CDx GI+BRCA status (n = 195). GI, genomic instability; PFS, progression-free survival.

Implementación de Plataforma local en España

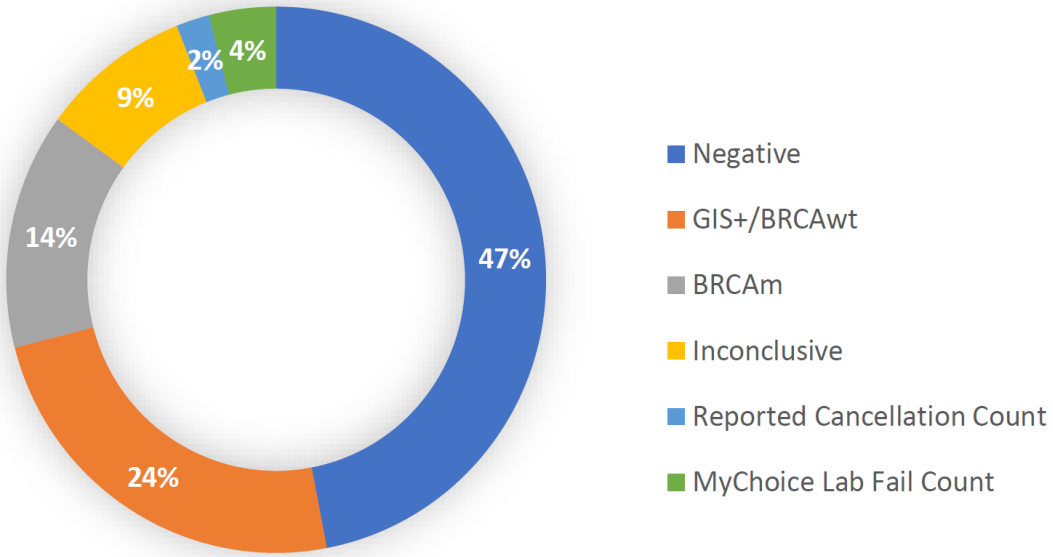
- Análisis de tejido tumoral
- Determinación de HRD mediante NGS (Sophia DDM HRD Solution o TSO500 Illumina)
- 4 centros:
  - ICO-HU. Bellvitge
  - H. Gral. Valencia
  - Fundación Jimenez Díaz
  - CHU Santiago

(+1 adicional en 2023 → H. Clínico San Carlos)

- Reporte de resultados estandarizado

Comparativa en vida real MMC vs Plataforma Local

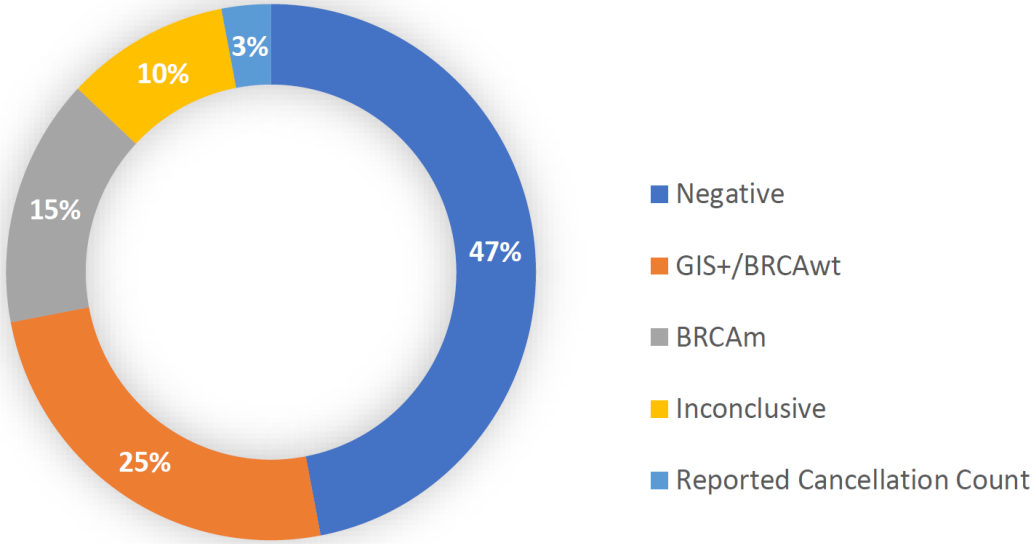
Myriad MyChoice



Periodo: Q2 2021-Q2 2022

N= 1322

Plataforma local



Periodo: Q2 2022-Q4 2022

N= 1075

Prevalencia de alteraciones en genes HRR *vs* GIS. Plataforma local

Resultados de 5 genes HRR

HRR Gene	Prevalencia	GIS +	GIS -	Comutaciones
CCNE1 Amplification	5,32% (43)	11,6% (5)	88,4% (38)	1 (BRCA2)
BRIP1	2,35% (19)	36,80%(7)	63,2% (12)	1 (PALB2)
PALB2	1,98% (16)	62,5%(10)	37,5% (6)	4 (BRCA1) 3 (BRCA2) 1 (Rad51c) 1(Rad51d)
Rad51c	1,11% (9)	33,3% (3)	66,6% (6)	1 (PALB2)
Rad51d	1,24% (10)	80% (8)	20% (2)	1 (PALB2)

N=807

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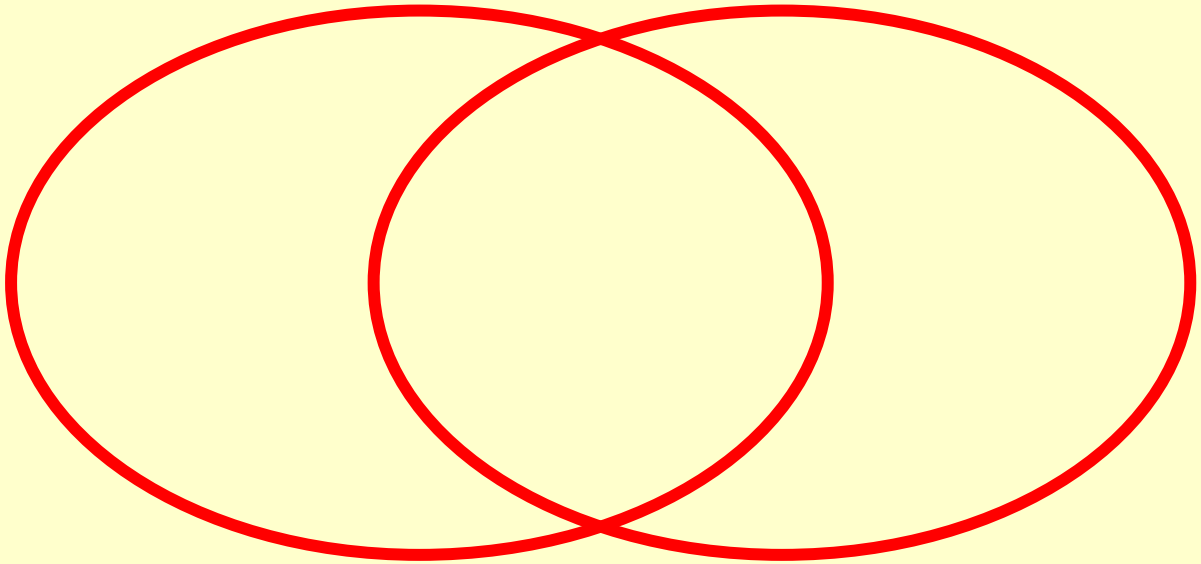
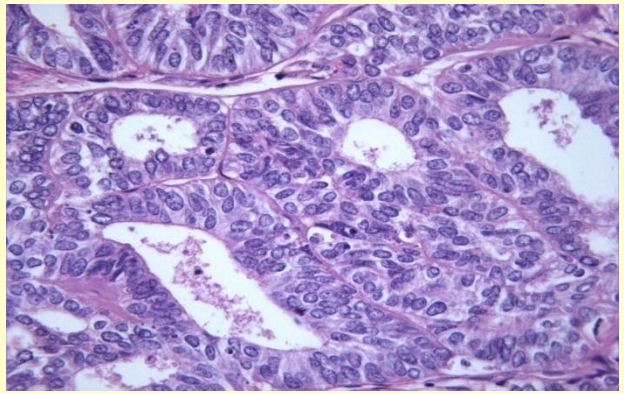
Molecular Pathology



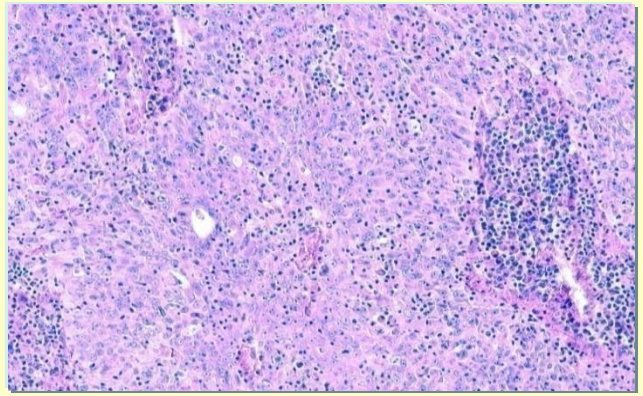
Morphology

Molecular Biology

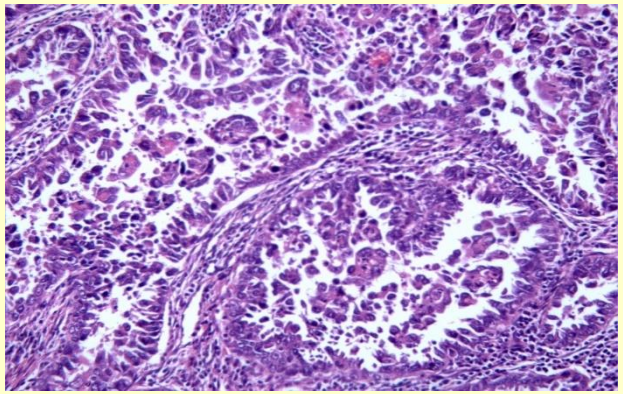
HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMA



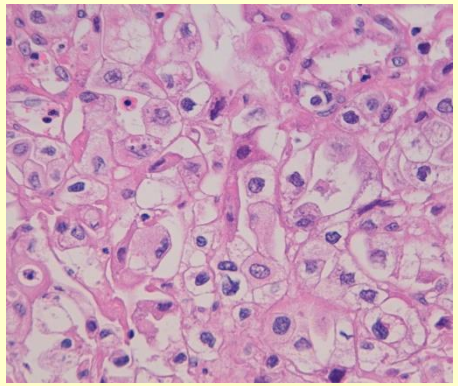
EEC 1,2



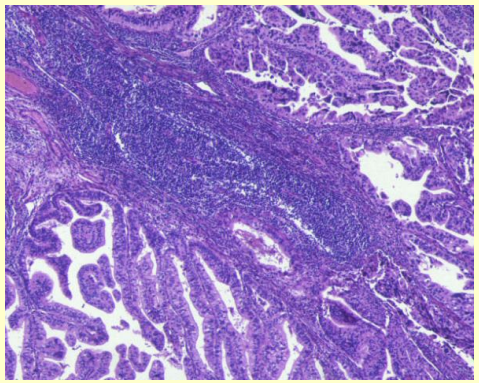
EEC 3



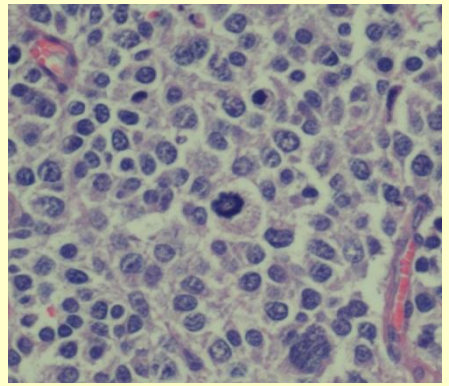
Serous



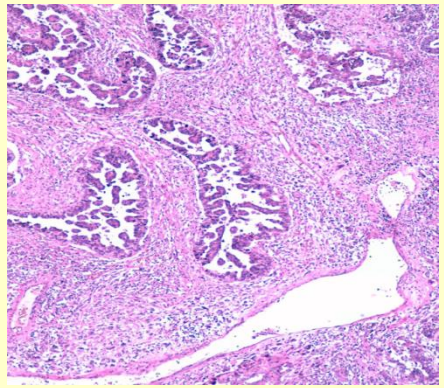
Clear Cell



Mixed



Undiff



Carcinosarcoma

Endometrioid and serous carcinomas have different abnormalities

Gene mutations in endometrioid endometrial carcinoma

GENE	FREQUENCY	GENE	FREQUENCY
PTEN *	77.7%	*MLL4*	9.1%
PIK3CA	53.1%	*BCOR*	8.0%
PIK3R1	37.1%	*ATR*	6.9%
CTNNB1	36.6%	*CCND1*	5.7%
ARID1A	35.4%	*SPOP*	5.7%
KRAS	24.6%	*SIN3A*	5.7%
CTCF	20.6%	*MKI67*	5.7%
RPL22	12.6%	*FBXW7*	5.1%
TP53	11.4%	*FOXA2*	5.1%
FGFR2	10.9%	*NRAS*	2.9%
ARID5B	10.9%		

**62/136 (45.5%) tumors with PTEN mutations has ≥ 2 mutations*

TCGA; Nature 2013

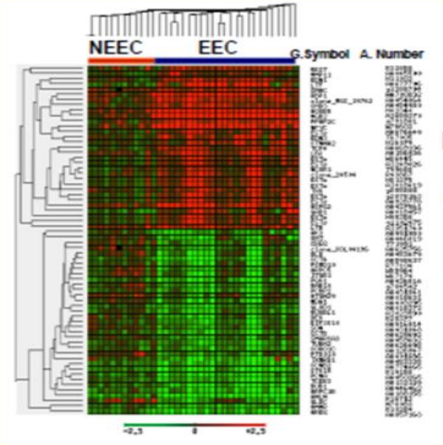
Gene mutations in serous endometrial carcinoma

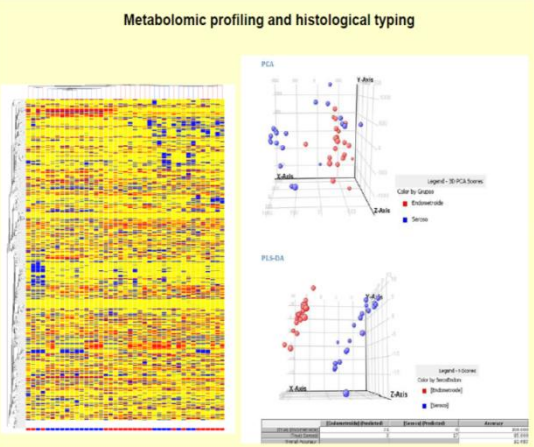
GENE	FREQUENCY	GENE	FREQUENCY
TP53	90.7%	*PRPF18*	7%
PIK3CA	41.9%	*SPOP*	7%
FBXW7	30.2%	*CDH19*	7%
PPP2R1A	36.6%	*FGFR2*	7%
CHD4	16.3%	*ARID1A*	7%
CSMD3	11.6%	*FOXA2*	4.6%
COLA11	11.6%	*USP36*	4.6%

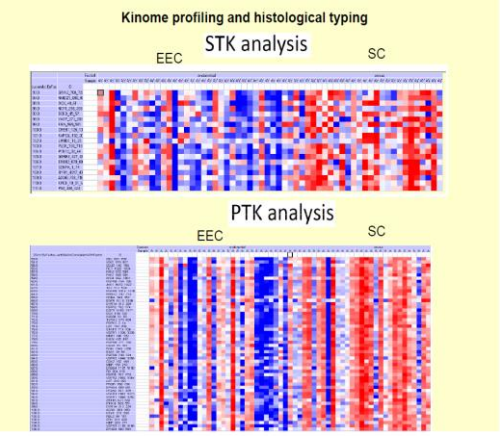
TCGA; Nature 2013

TAF1 (30%), *EP300* (8%), *TSPYL2* (6%), *MAP3K4* (6%) and *ABCC9* (6%).

Khun et al; J Nati Cancer Inst 2012.
Le Gallo et al; Nat Genet 2012;
Zhao et al; PNAS 2013.

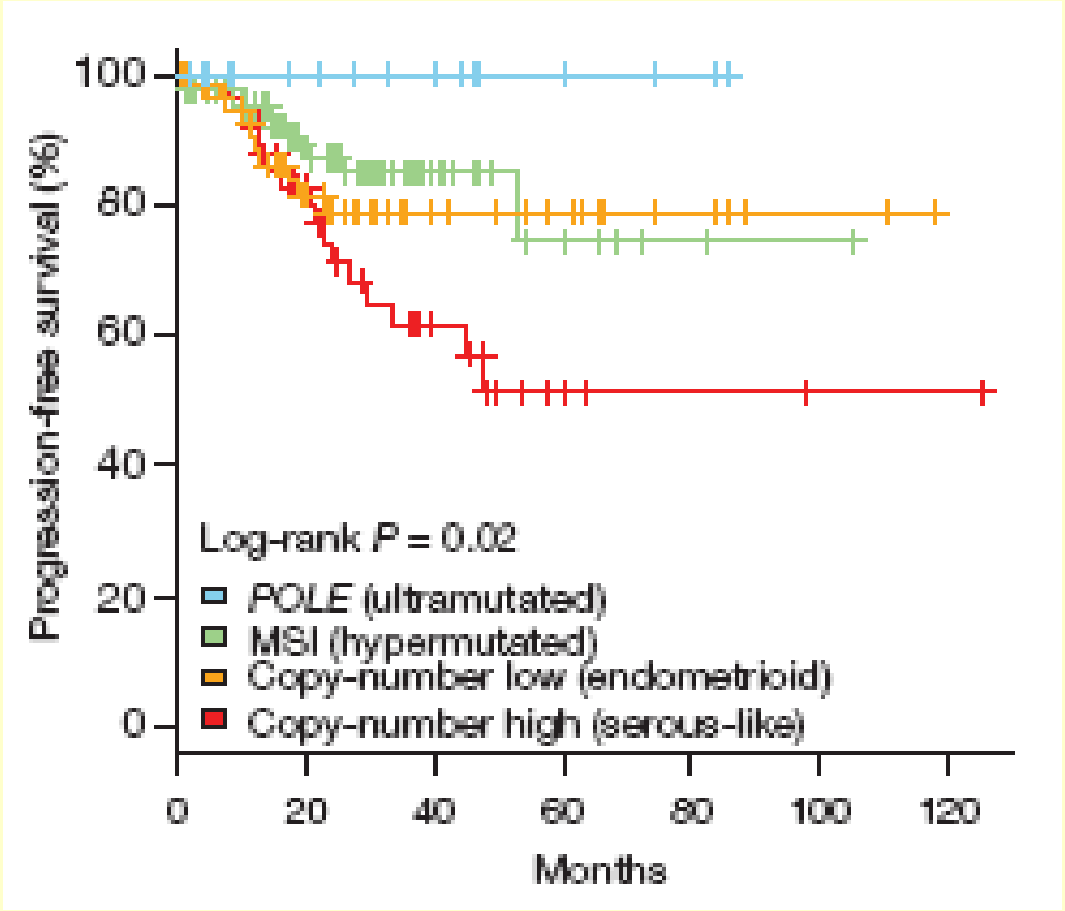






Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*



Molecular classification is a good prognostic risk stratification similar to what has been found in other types of tumor

1- High mutation burden correlates with good prognosis in pancancer studies

2- High copy number variation correlates with bad prognosis in pancancer studies

3- Molecular classification does not have a good correlation with risk-factors, precursor lesions, and pathogenesis.

Bringing TCGA subtyping into pathology in high-grade endometrial carcinomas

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POLE wild-type, p53 wild-type pattern, normal mismatch repair	**EEC with low copy number alterations**
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ESGO-ESTRO-ESP and ESMO Guidelines Endometrial Cancer

Virchows Archiv (2021) 478:153–190
https://doi.org/10.1007/s00428-020-03007-z

ORIGINAL ARTICLE

ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma

Nicole Concin[1,2] · Carien L. Creutzberg[3] · Ignace Vergote[4] · David Cibula[5] · Mansoor Raza Mirza[6] · Simone Marnitz[7] · Jonathan A. Ledermann[8] · Tjalling Bosse[9] · Cyrus Chargari[10] · Anna Fagotti[11] · Christina Fotopoulou[12] · Antonio González-Martín[13] · Sigurd F. Lax[14,15] · Domenica Lorusso[11] · Christian Marth[16] · Philippe Morice[17] · Remi A. Nout[18] · Dearbhaile E. O'Donnell[19] · Denis Querleu[11,20] · Maria Rosaria Raspollini[21] · Jalid Sehouli[22,23] · Alina E. Sturdza[24] · Alexandra Taylor[25] · Anneke M. Westermann[26] · Pauline Wimberger[27] · Nicoletta Colombo[28] · François Planchamp[29] · Xavier Matias-Guiu[30,31]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. Oaknin[1], T. J. Bosse[2], C. L. Creutzberg[3], G. Giornelli[4], P. Harter[5], F. Joly[6,7], D. Lorusso[8,9], C. Marth[10], V. Makker[11,12], M. R. Mirza[13], J. A. Ledermann[14,15] & N. Colombo[16,17], on behalf of the ESMO Guidelines Committee*

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]

Bringing TCGA subtyping into pathology in high-grade endometrial carcinomas

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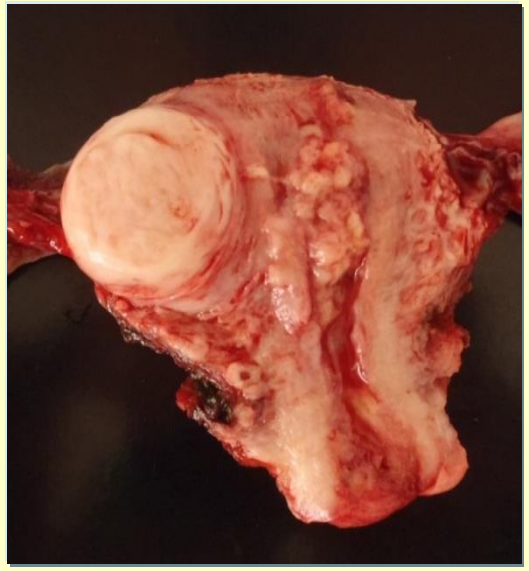
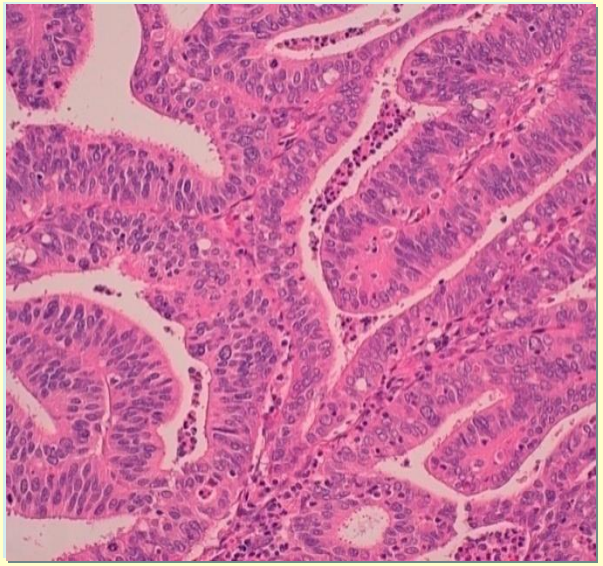
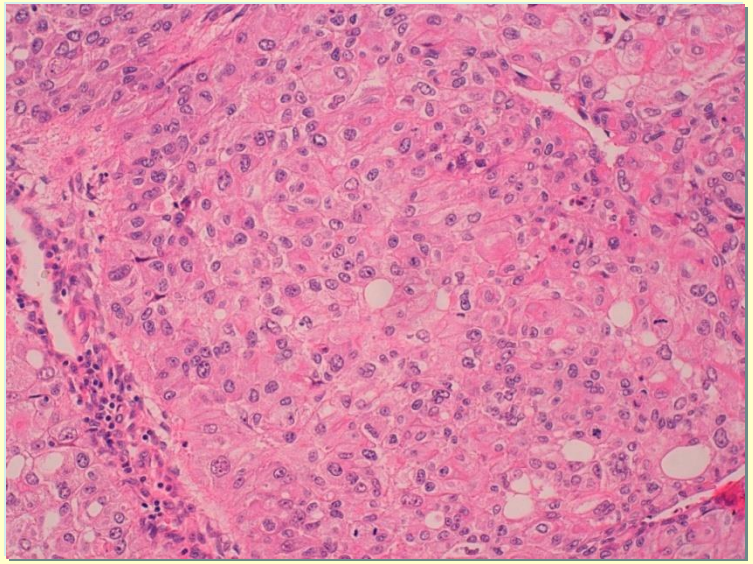
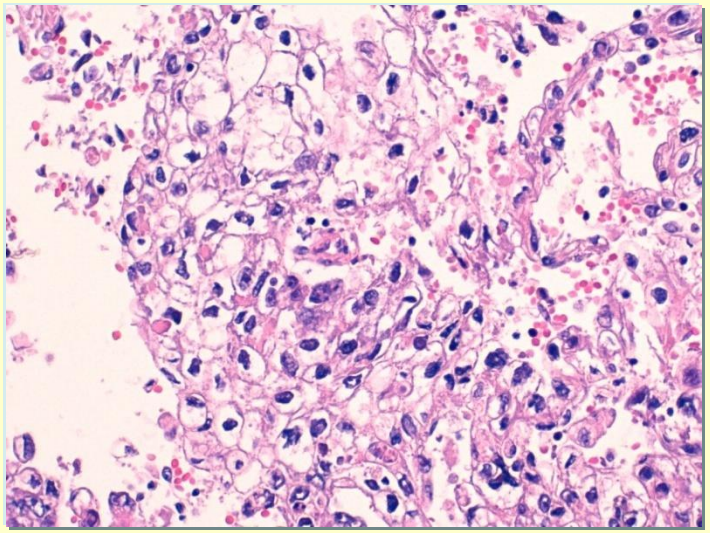
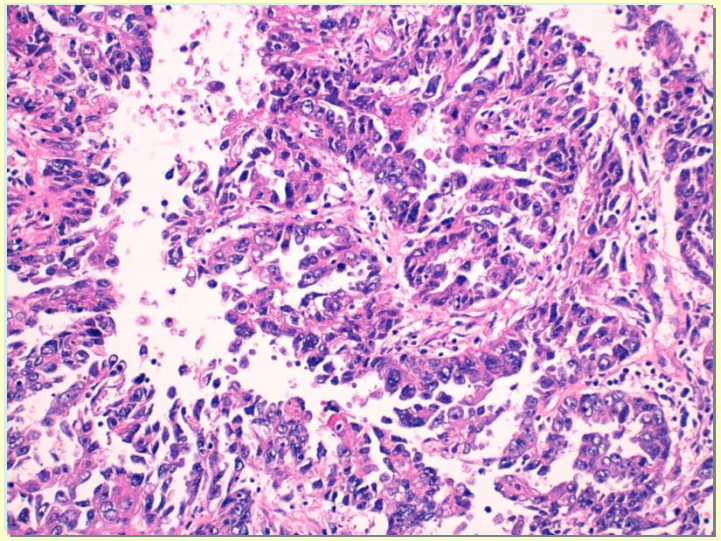
Heterogenous POLE-mutated EC

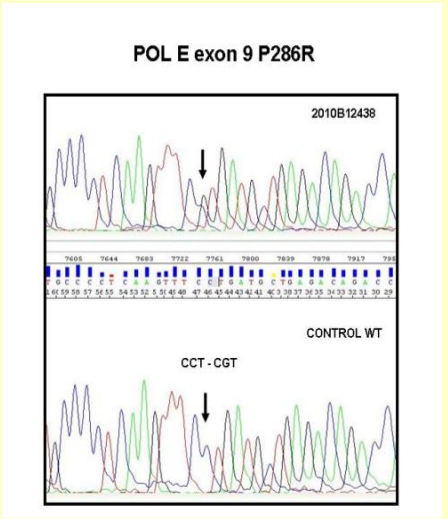












Bringing TCGA subtyping into pathology in high-grade endometrial carcinomas

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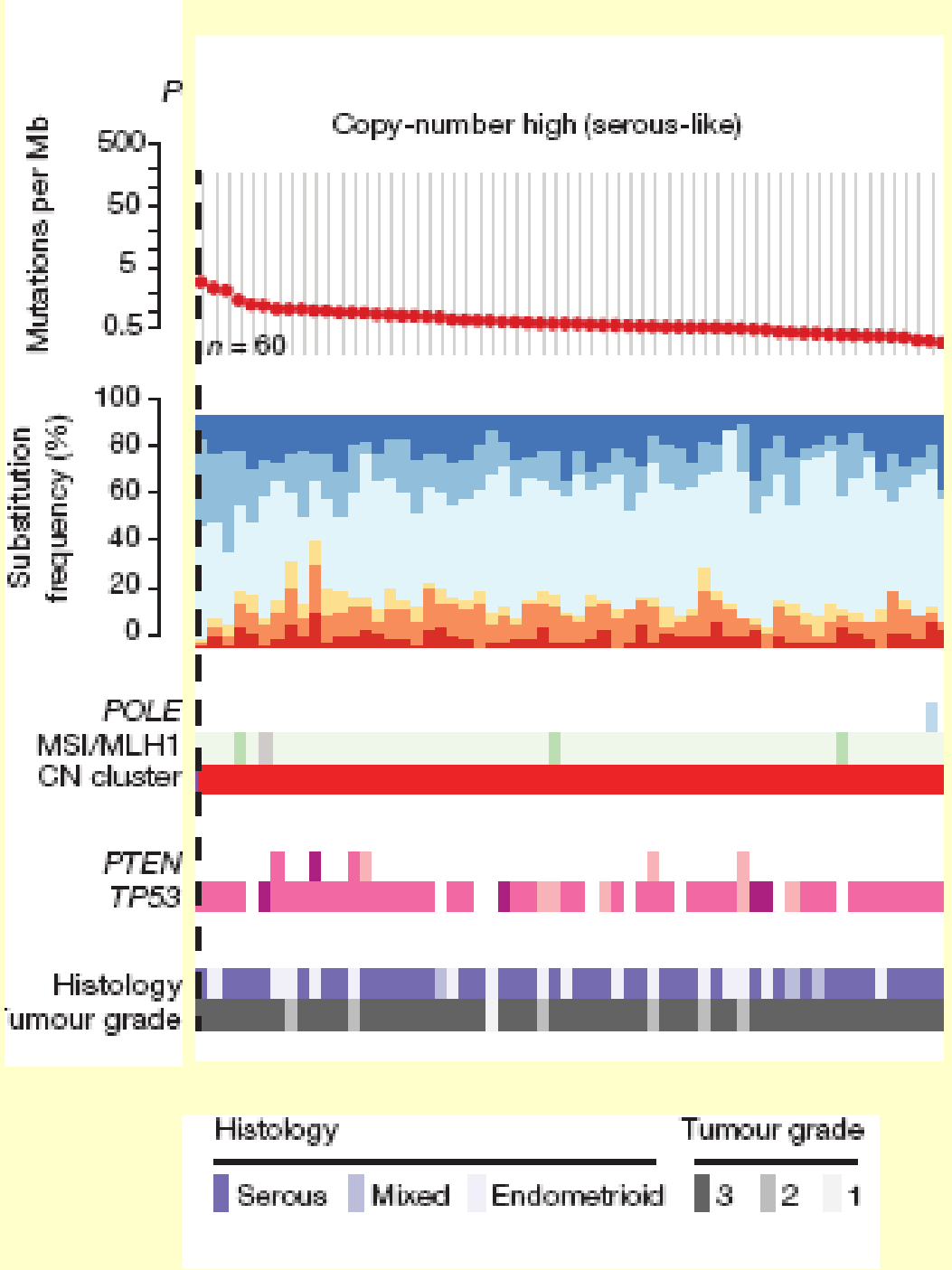
POLE wild-type, p53 wild-type pattern, normal mismatch repair	**EEC with low copy number alterations**
POLE wild-type, p53 abnormal expression:	**EEC with high copy number alterations**

Group 4, Serous-like tumors

Serous (94%), mixed ca (62%), endometrioid ca (12%, usually grade 3) with p53 mutations and recurrent amplifications (MYC, ERBB2, CCNE1, FGFR3, SOX17)



Original Article

Equivalent Survival of p53 Mutated Endometrial Endometrioid Carcinoma Grade 3 and Endometrial Serous Carcinoma

Mary Anne Brett, M.D., Eshetu G. Atenafu, Ph.D., Nilanchali Singh, M.D., Prafull Ghatage, M.D., Blaise A. Clarke, M.D., Gregg S. Nelson, M.D., Ph.D., Marcus Q. Bernardini, M.D., and Martin Köbel, M.D.

. There was no significant difference in survival between ESC and p53 mutated EEC3 in multivariable analysis.

. Although this is so, separate classification should continue due to biological differences that will become important for future targeted therapy.

Clinicopathologic Analysis of 187 High-grade Endometrial Carcinomas of Different Histologic Subtypes: Similar Outcomes Belie Distinctive Biologic Differences

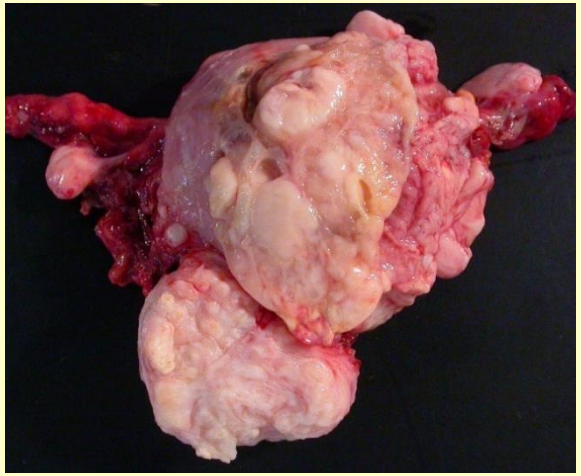
Robert A. Soslow, MD, John P. Bissonnette, MD,† Andrew Wilton, MD,‡ Sarah E. Ferguson, MD,§ Kaled M. Alektiar, MD,‖ Linda R. Duska, MD,¶ and Esther Oliva, MD†*

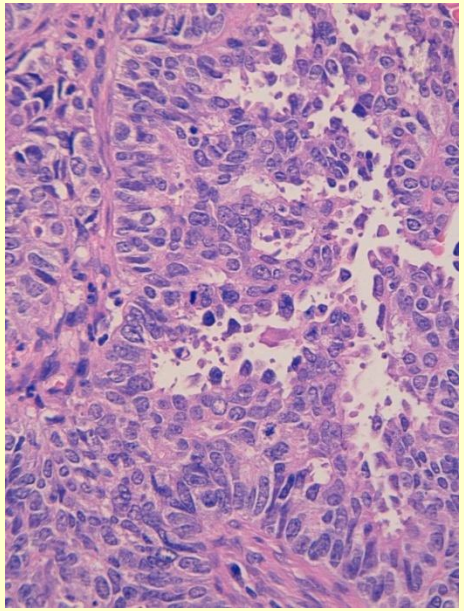
Age/type	Endometrioid n = 89	Serous n = 61
≤65	55%	34%
> 65	45%	66%

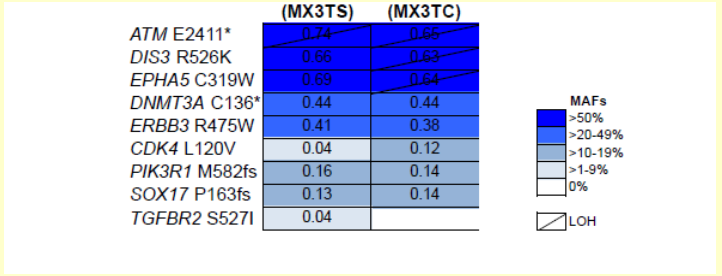
Hyperplasia/type	Endometrioid n = 66	Serous n = 42
No	83%	98%
Yes	17%	2%

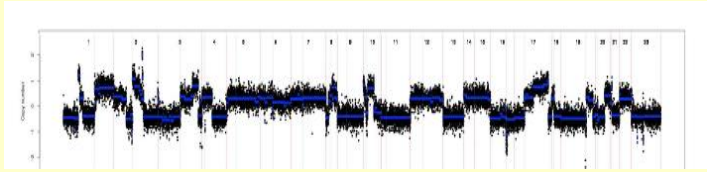
Peritoneal Mets/Type	Endometrioid n = 70	Serous n = 53	*P*
No	90%	60%	0.0001
Yes	10%	40%	

An example of p53 wild type serous carcinoma









Microscopy: Serous carcinoma

TCGA by exome sequencing: High copy number, serous-like ca

TCGA by TCGA surrogate: Low copy number EC

Conclusion: Serous ca, serous-like but with wild-type p53

Bringing TCGA subtyping into pathology in high-grade endometrial carcinomas

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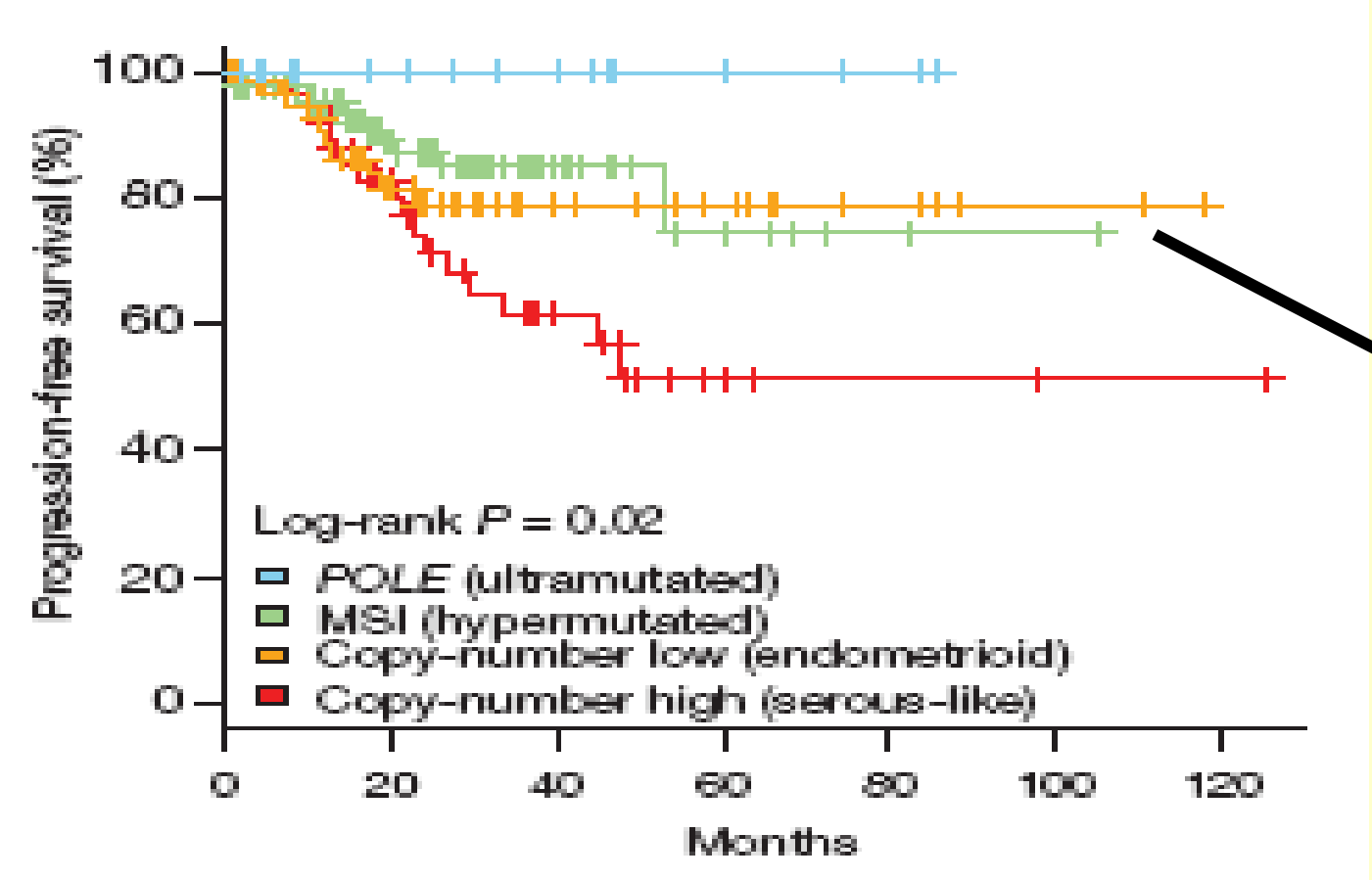
Endometrial carcinoma
TCGA



Potential markers to stratify patients in the dMMR-MSI group:

- MMR gene mutations versus MLH-1 promoter methylation
- Differences in TMB
- Secondary alterations (JAK1)
- Subclonality
- Different immune microenvironment

Speaker experience (Prof. Xavier Matias-Guiu, University of Lleida, Spain).

Bringing TCGA subtyping into pathology in high-grade endometrial carcinomas

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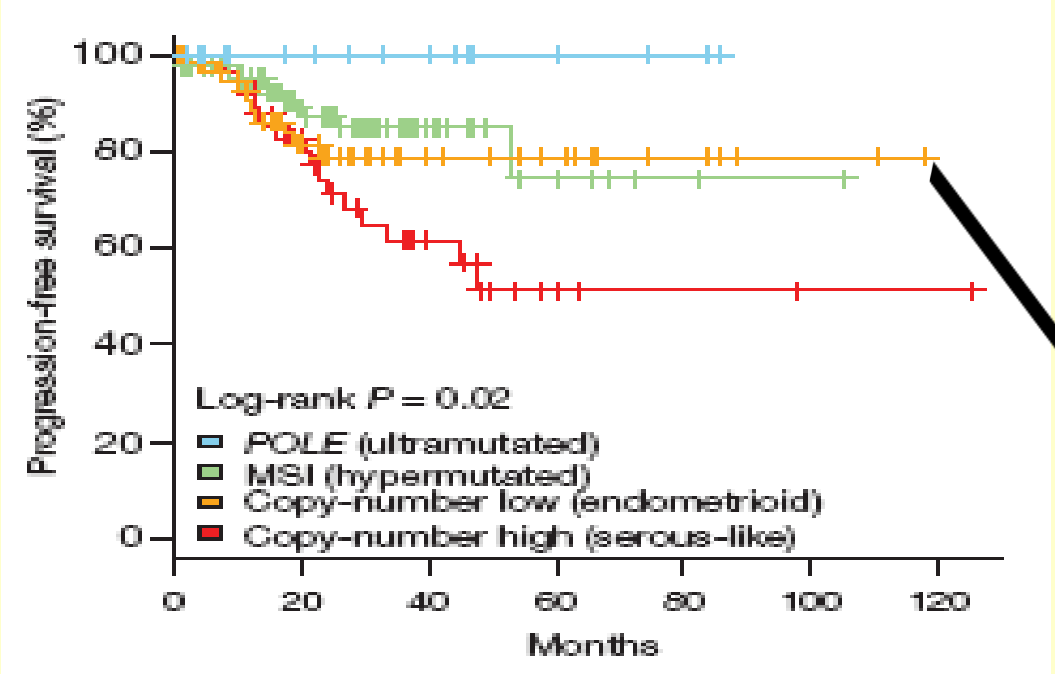
Endometrial carcinoma
TCGA, 2013



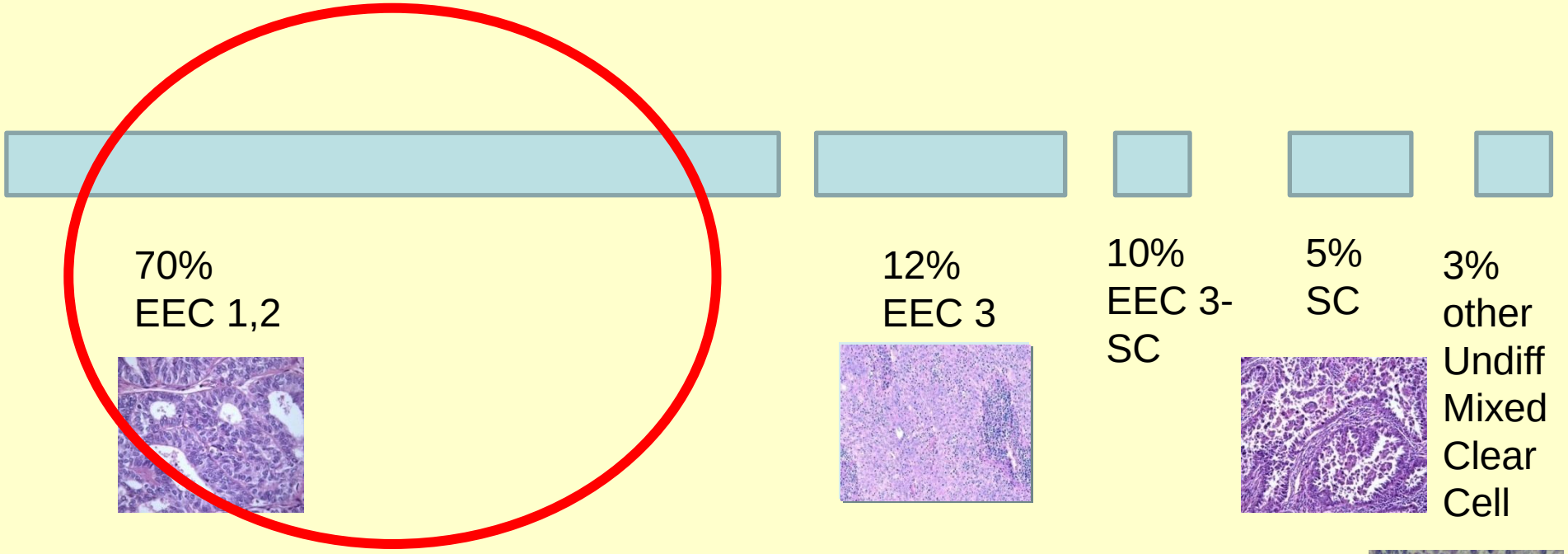
Potential markers to stratify patients in the LCN-NSMP group:

Estrogen receptor status
L1CAM
CTNNB1 (beta-catenin) mutations

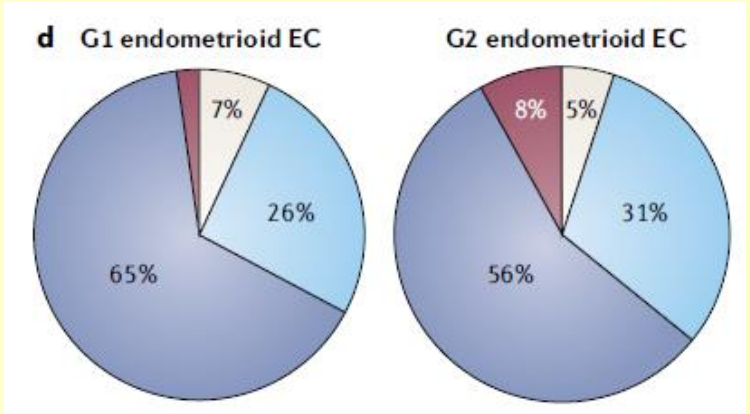
Histologic grade

Histologic type (ex: Mesonephric-like carcinomas)

IS MICROSCOPIC EXAMINATION USEFUL IN THE TIMES OF MOLECULAR CLASSIFICATION OF ENDOMETRIAL CARCINOMA?



IS MOLECULAR CLASSIFICATION HELPFUL IN THE BIG GROUP OF EEC1,2 ?



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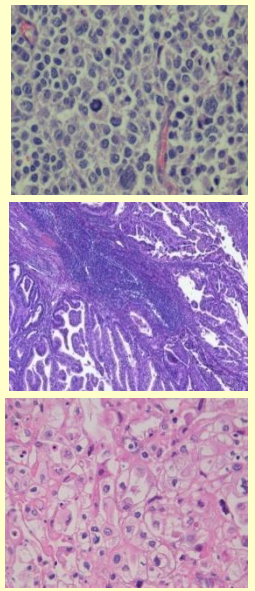


Gynecologic and Obstetric Pathology **Included with On Demand**

Molecular Landscape and Clinical Behavior of Stage I p53-Abnormal Low-Grade Endometrioid Endometrial Carcinomas

Tue, March 14

CC Room 217

Lisa Vermij: None; Amy Jamieson: None; Joseph Carlson: None; Brooke Howitt: None; Philip Ip: None; Sigurd Lax: None; Glenn McCluggage: None; Naveena Singh: None; Jessica McAlpine: None; Remi Nout: None; Carien Creutzberg: None; Nanda Horeweg: None; Tjalling Bosse: None; C. Blake Gilks: None

Cohort selection

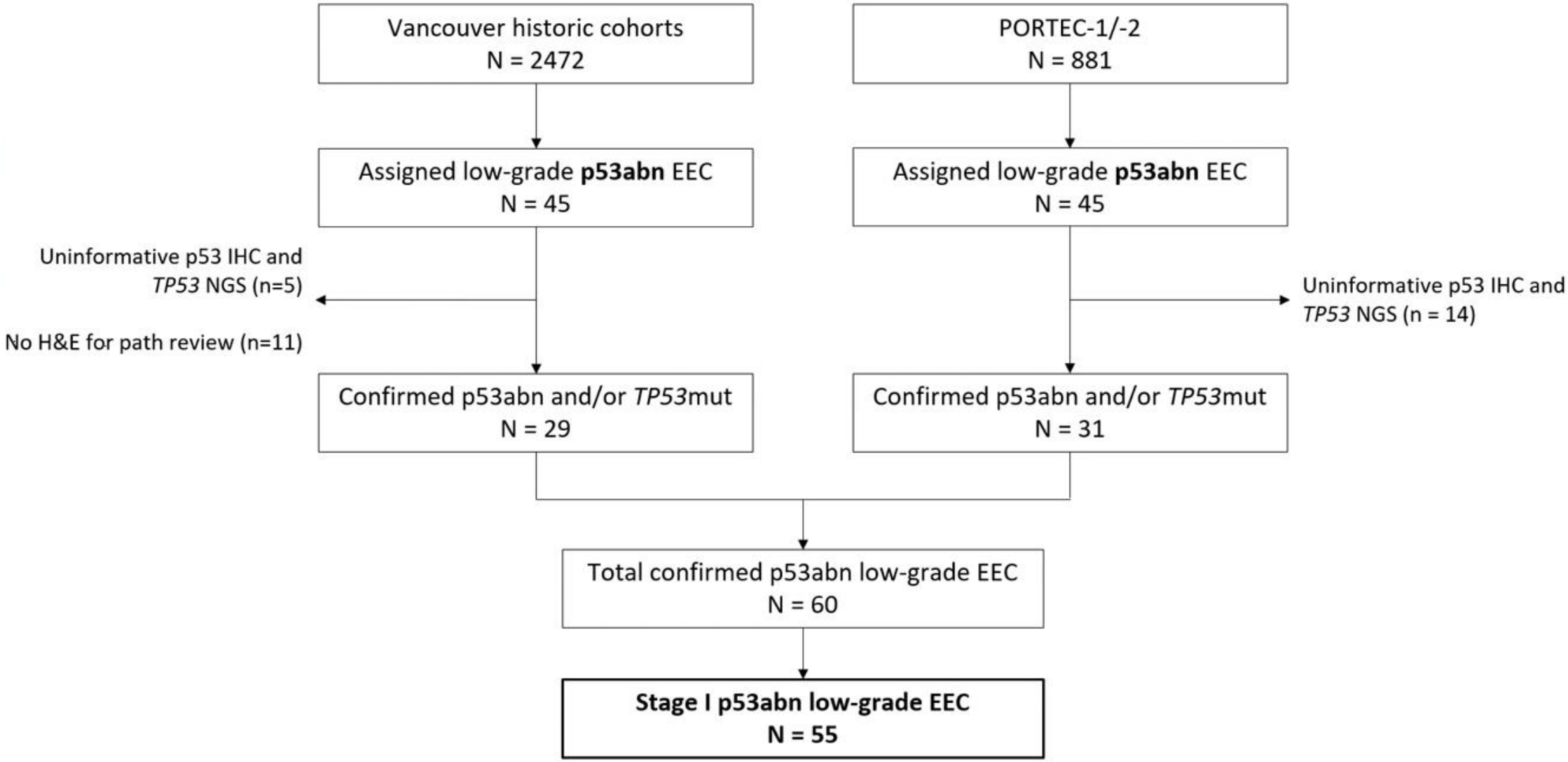
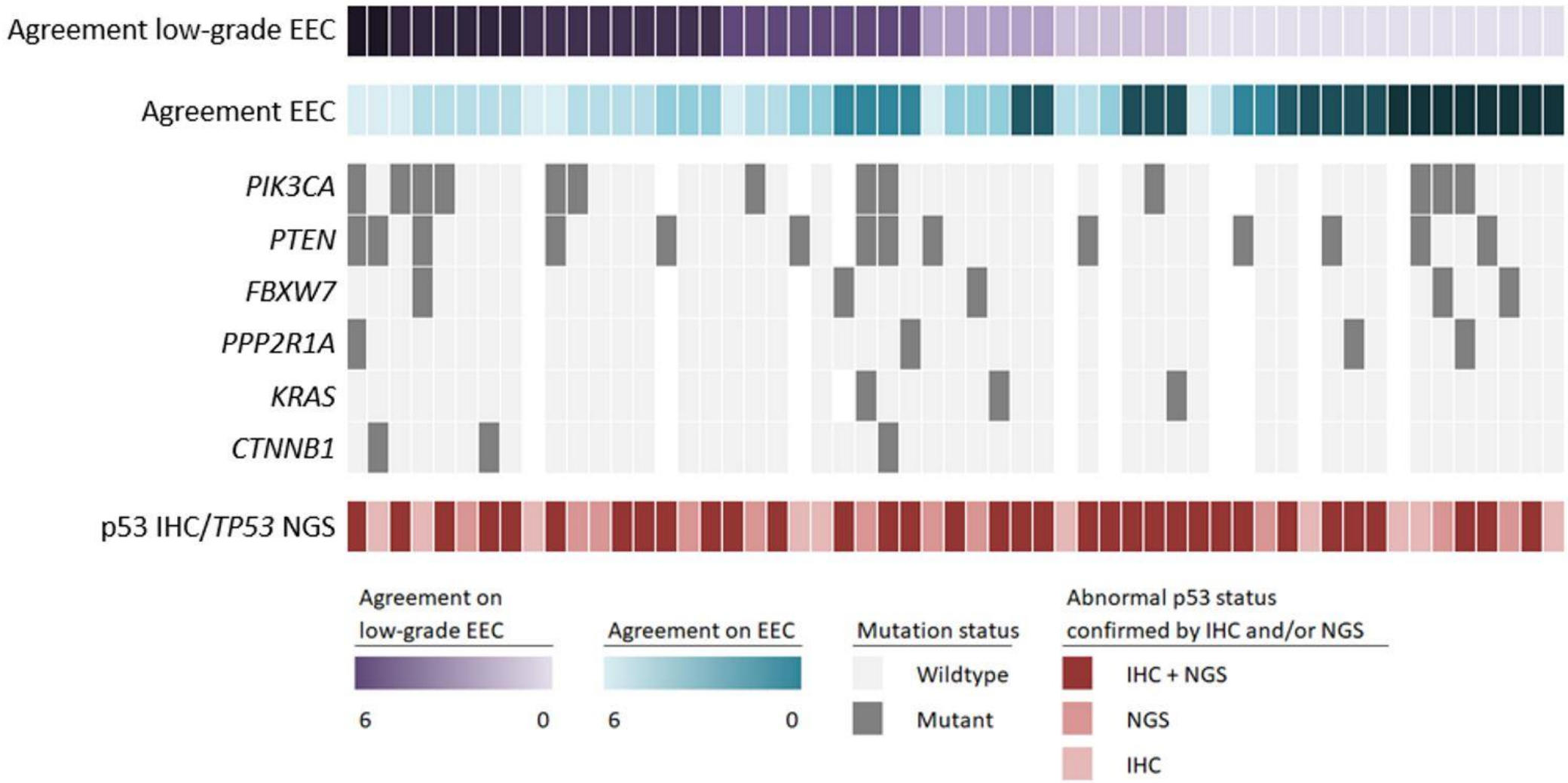
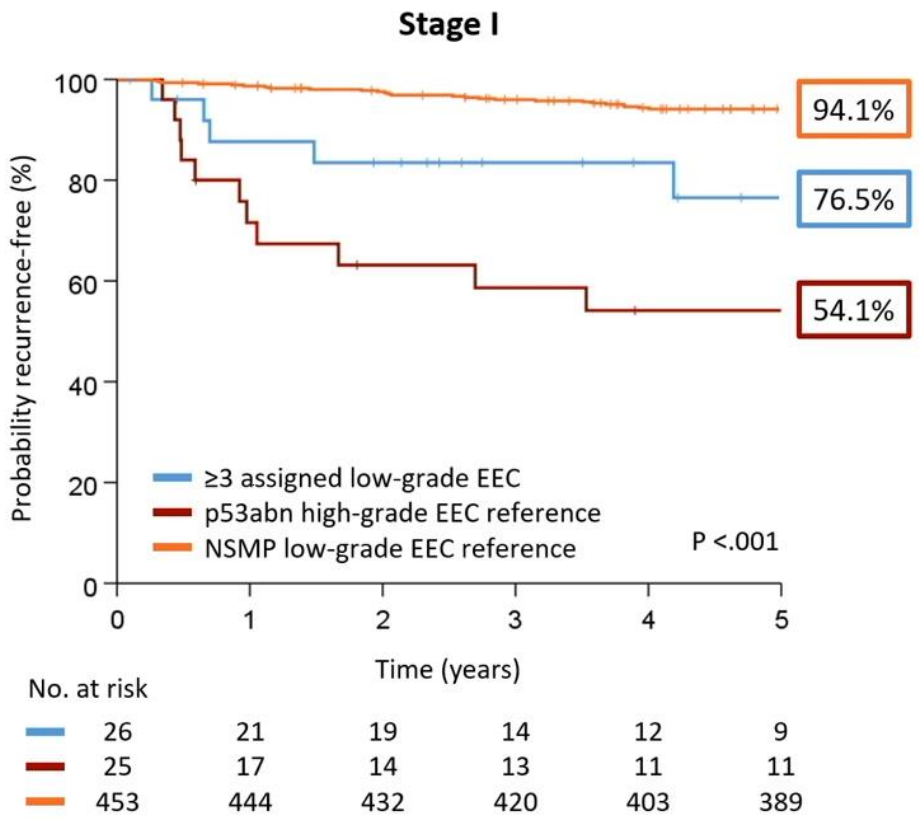


Figure 2. Molecular landscape of 55 stage I p53-abnormal endometrioid endometrial carcinomas (EEC), clustered by the degree of agreement on low-grade EEC histology by expert pathologists.

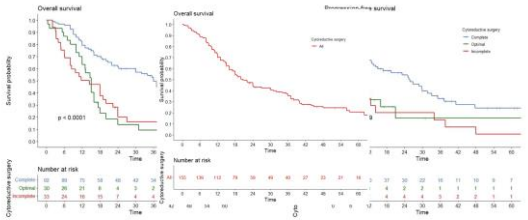


Significant risk of recurrence for stage I p53abn low-grade EEC



Conclusion:

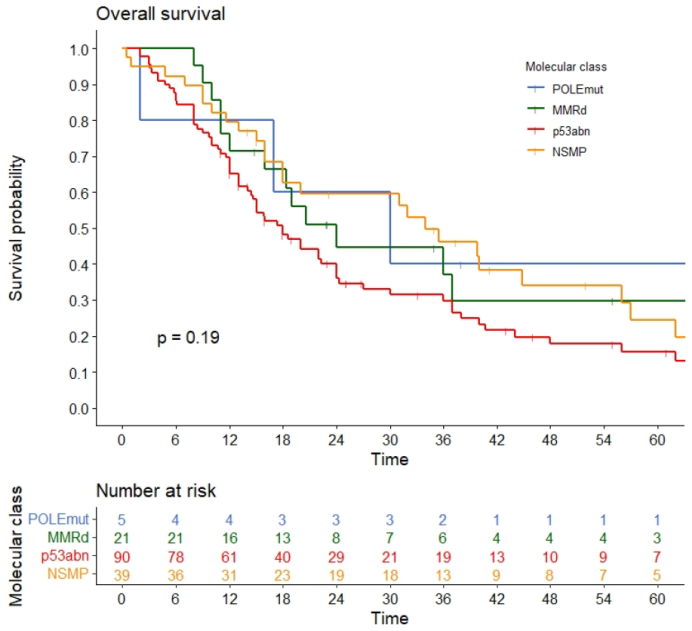
A subset of p53abn endometrial carcinomas are morphologically low-grade endometrioid with a molecular landscape that is similar to prototypical p53abn endometrial carcinomas. The risk of recurrence for patients with stage I low-grade p53abn EEC is higher compared to the risk of recurrence of stage I low-grade EEC in literature. Our results may support performing molecular classification on all endometrial carcinomas.

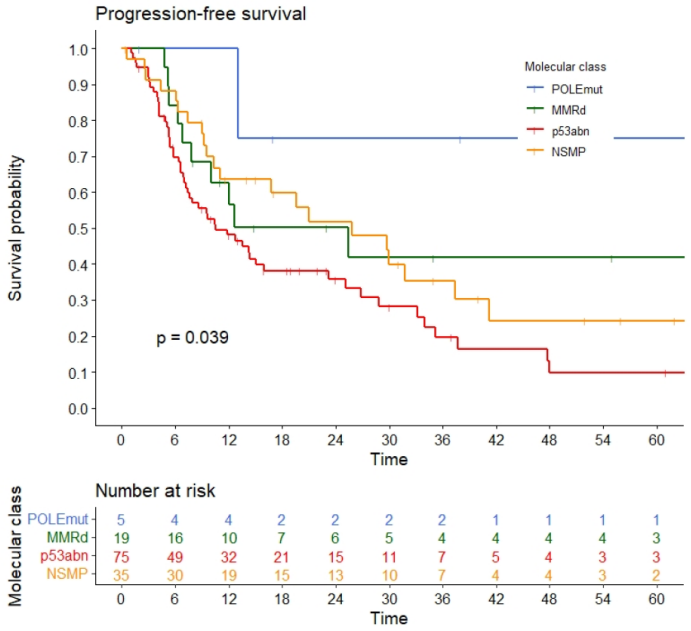


→ 5-year survival surgically treated stage IV EC 26.5%

	Stage I endometrial cancer (PORTEC 1 and 2 trial, N=695)	Stage I-III high risk endometrial cancer PORTEC-3 trial (N=410)	Stage IV endometrial cancer (N=156)
***POLE*mut**	37 (5.5%)	51 (12.4%)	5 (3.2%)
MMRd	200 (29.6%)	137 (33.4%)	21 (13.5%)
P53abn	49 (7.3%)	93 (22.7%)	91 (58.3%)
NSMP	389 (57.6%)	129 (31.5%)	39 (25%)

→ Distribution molecular classification of stage IV EC patients different compared to earlier stage EC





→ *POLE* mutant stage IV EC patients better PFS

→ Further molecular classification does not influence OS

ARTICLE

https://doi.org/10.1038/s41467-020-18819-5 OPEN

Molecular stratification of endometrioid ovarian carcinoma predicts clinical outcome

Robert L. Hollis[1,5], John P. Thomson[1,5], Barbara Stanley[1,5], Michael Churchman[1], Alison M. Meynert[2], Tzyvia Rye[1], Clare Bartos[1], Yasushi Iida[1,3], Ian Croy[1], Melanie Mackean[4], Fiona Nussey[4], Aikou Okamoto[3], Colin A. Semple[2], Charlie Gourley[1,6] & C. Simon Herrington[1,6]✉

Molecular-based classification algorithm for endometrial carcinoma categorizes ovarian endometrioid carcinoma into prognostically significant groups

Carlos Parra-Herran[1,2], Jordan Lerner-Ellis[2,3,4], Bin Xu[1,2], Sam Khalouei[3], Dina Bassiouny[1,5], Matthew Cesari[1,2], Nadia Ismiil[1,2] and Sharon Nofech-Mozes[1,2]

Molecular Heterogeneity of Endometrioid Ovarian Carcinoma

An Analysis of 166 Cases Using the Endometrial Cancer Subrogate Molecular Classification

Susanna Leskela, PhD,† Ignacio Romero, MD,‡ Juan M. Rosa-Rosa, PhD,*† Tamara Caniego-Casas, MSc,*† Eva Cristobal, PhD,*† Belén Pérez-Mies, MD, PhD,†§ Ana Gutierrez-Pecharroman, MD,§ Almudena Santón, PhD,†§ Belén Ojeda, MD, PhD,‖ Raquel López-Reig, MSc,¶ María L. Palacios-Berraquero, MD,# Encarna Andrada, MD,** Santiago Montes, MD,†† Francisco Pastor, MD,‡‡ Maria C. Gomez, MD,§§ José A. López-Guerrero, PhD,¶ Andrés Poveda, MD,‖‖ and José Palacios, MD, PhD*†§¶¶*

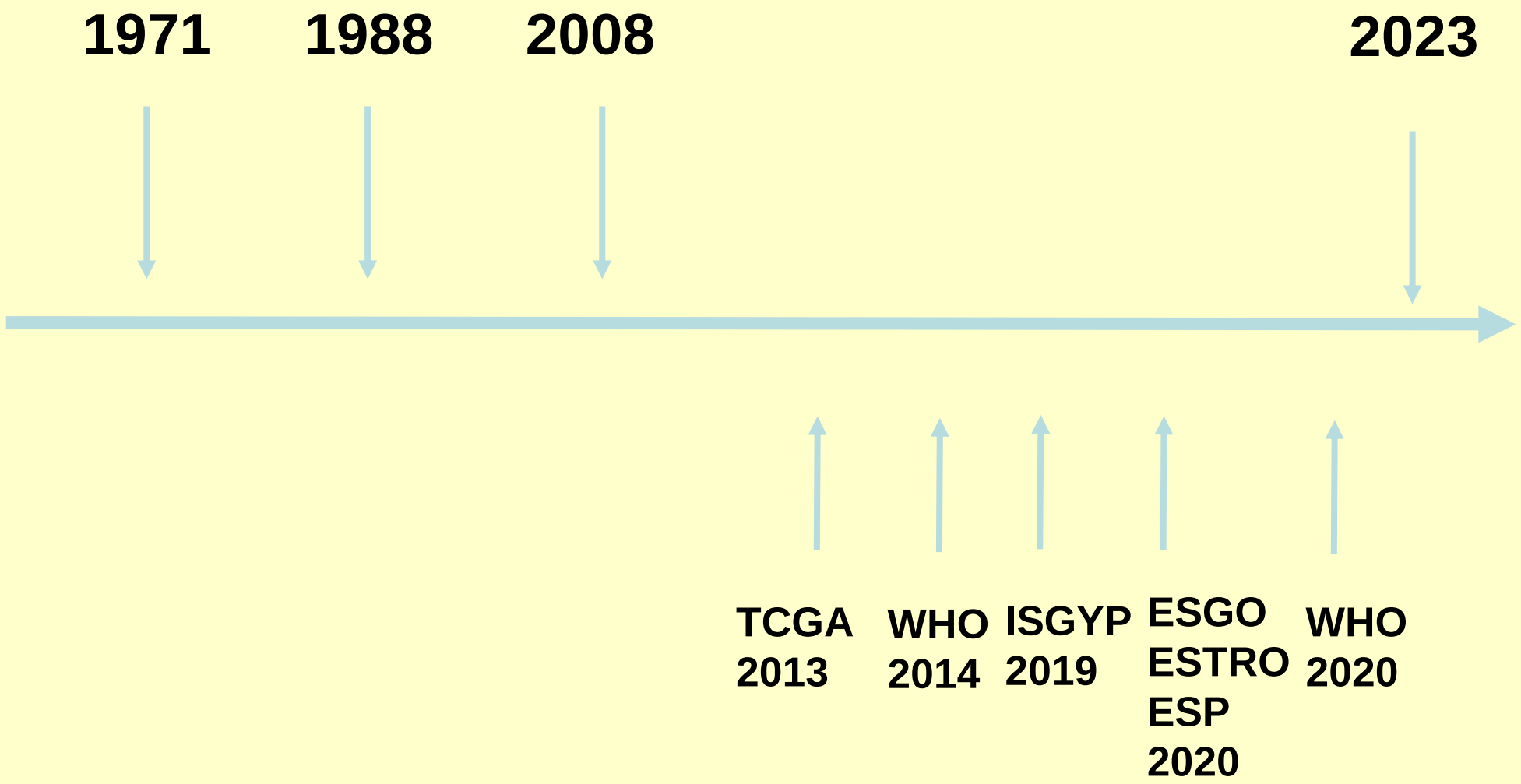
Hollis, et al. Nat Commun. 2020 Oct 5;11(1):4995.
Parra-Herran, et al. Mod Pathol. 2017 Dec;30(12):1748-1759.
Leskela, et al. Am J Surg Pathol. 2020 Jul;44(7):982-990.

Outline

1- Molecular risk stratification in ovarian cancer

2- Update on the molecular classification of endometrial cancer

3- Incorporation of molecular data into staging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ISGYP
2019
ESGO
ESTRO
ESP
2020
WHO
2020

- Multidisciplinary team
- Gynecological cancer societies liaisons
- Alignement with AJCC and IJCC
- ESGO-ESTRO-ESP guideline as a template
- In pathology, take into consideration previous consensus guidelines (ISGYP, WHO)
- ISGYP surveys

- FIGO Endometrial Cancer Staging Subcommittee

Members

Jonathan Berek (JB), Carien Creutsfeld (CC), Christina Fotopoulou (CF), Xavier Matias-Guiu (XM), David Mutch (DM), David Gaffney (DG) , Nicole Concin (NC), Kristina Lindemann (KL) ,

Olivia Bruce (OB) – IGO HQ, Lily Martins (LM) – FIGO HQ

BREAST AJCC

AJCC ANATOMIC AND PROGNOSTIC STAGE GROUPS

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T) – Clinical and Pathological

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm).
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see section "Rules for Classification")

**Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th Edition.*

Definition of Regional Lymph Nodes – Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases;
	or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Definition of Regional Lymph Nodes – Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

*Note that imaging studies are not required to assign the cM0 category

for patients who have surgery as initial treatment and therefore have pathological T and N information. Patients treated with neoadjuvant therapy should have clinical prognostic stage and the observed degree of response to treatment recorded, but are not assigned pathological prognostic stage.

The Anatomic Stage Group table should only be used in regions of the world where tumor grading and/or biomarker testing for HER2, ER and PR are not routinely available. For worldwide comparison, the Anatomic Stage Group can be back-calculated from U.S. registries from the recorded T, N, and M categories.

AJCC Anatomic Stage Groups

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.

Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Notes:
1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0	G1	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IA
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0	G1	Positive	Positive	Positive	IB
T1* N1** M0				Negative	IIA
T2 N0 M0			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0	G1	Positive	Positive	Positive	IB
T3 N0 M0				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0	G1	Positive	Positive	Positive	IIA
T1* N2 M0				Negative	IIIA
T2 N2 M0			Negative	Positive	IIIA
T3 N1*** M0				Negative	IIIA
T3 N2 M0		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0	G1	Positive	Positive	Positive	IIIA
T4 N1*** M0				Negative	IIIB
T4 N2 M0			Negative	Positive	IIIB
Any T N3 M0				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

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Review Article

FIGO Staging of Endometrial Adenocarcinoma: A Critical Review and Proposal

Richard J. Zaino, M.D.

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SPECIAL ARTICLE
Gynecology

WILEY

A proposal for updating the staging of endometrial cancer

Amita Maheshwari[1] | Sudeep Gupta[2] | Jaime Prat[3,*]

- *Barlin JN, Soslow RA, Lutz M, Zhou QC, St Clair CM, Leitao MM Jr, Iasonos A, Hensley ML, Barakat RR, Matias-Guiu X, Abu-Rustum NR*
- Redefining Stage I Endometrial Cancer: Incorporating Histology, a Binary Grading System, Myometrial Invasion, and Lymph Node Assessment.
- *Int J Gynecol Cancer. 2013 23:1620-8*

Best Practice & Research Clinical Obstetrics and Gynaecology 29 (2015) 776–789

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journal homepage: www.elsevier.com/locate/bpobgyn

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Molecular staging of gynecological cancer: What is the future?☆

Pratibha S. Binder, MD, Gynecologic Oncology Fellow [a,*], Jaime Prat, MD, Professor [b], David G. Mutch, MD, Professor [a]

Endometrial Cancer Staging, Improvement areas, Surveys

Survey goals: To understand **pathologists' and clincians' perceptions of the most clinically relevant issues in the current FIGO endometrial cancer staging criteria that merit improvement or refinement.**

Survey creators: Xavier Matias-Guiu, Joe Rabban, Naveena Singh

Survey intended participants: All standard members of ISGyPs and IGCS.

Survey tool: The surveys are created as a Google Form. A hyperlink will be emailed to the participants.

Requirement for complete responses: The Google Form is designed to require the responder to complete the entire survey. The Google Form will not register incomplete surveys.

Table 1: Demographics of both groups

Current practice setting		
	Pathologists # (%)	Clinicians # (%)
Academic institution	106 (62)	74 (55)
Tertiary care hospital (no academic affiliation)	17 (10)	15 (11)
Public hospital (no academic affiliation)	17 (10)	9 (7)
Private practice	11 (6)	23 (17)
Retired	3 (2)	3 (2)
In training	9 (5)	5 (4)
Other	9 (5)	6 (4)

Question	Pathologists %	Clinicians %	P value
Histology-Morphology			
Do you think tumor histologic type should be incorporated into staging criteria (such as by a sub-stage category) ?			0.1
Yes	52	65	
No (total)	38	32	
I don't know	10	3	

Do you think tumor molecular classification (TCGA categories) should be incorporated into staging criteria (such as by a sub-stage category) ?			0.08
Yes	48	63	
No (total)	37	30	
I don't know	15	7	

Do you think lymphovascular space invasion should be incorporated in staging?			0.03*
Yes	48	61	
No (total)	42	33	
I don't know	10	6	

Do you think lymph node involvement should be sub-staged as macro-metastases, micro-metastases, isolated tumor cells?			0.3
Yes	72	79	
No (total)	24	20	
I don't know	4	1	

Do you think that synchronous involvement of endometrium and ovaries by endometrioid carcinoma should be assigned as stage III endometrial cancer?			0.3
Yes	60	53	
No (total)	37	42	
I don't know	3	5	

Main changes in FIGO staging 2023

- Incorporation of molecular classification, when feasible.
- Incorporation of histogical types
- Incorporation of LVSI.
- Specific substaging for “synchronous” endometrioid and ovarian carcinoma
- LN staging incorporate the concept of macro and micrometastasis and ITC
- Distinction between pelvic and abdominal peritoneal involvement

Outline

1- Molecular risk stratification in ovarian cancer

2- Update on the molecular classification of endometrial cancer

3- Incorporation of molecular data into staging

Integrando la biología molecular en la anatomía patológica en tumores ginecológicos

Xavier Matias-Guiu, Hospital U Arnau de Vilanova, Hospital U de Bellvitge, Universities of Lleida and Barcelona, IRBLLEIDA, IDIBELL.