
SACRO CUORE DON CALABRIA IRCCS

1922 - 2022 SACRO CUORE

# Carcinoma ovarico: l'evoluzione delle conoscenze in ambito diagnostico-terapeutico

## Il Ruolo dell'Anatomo Patologo

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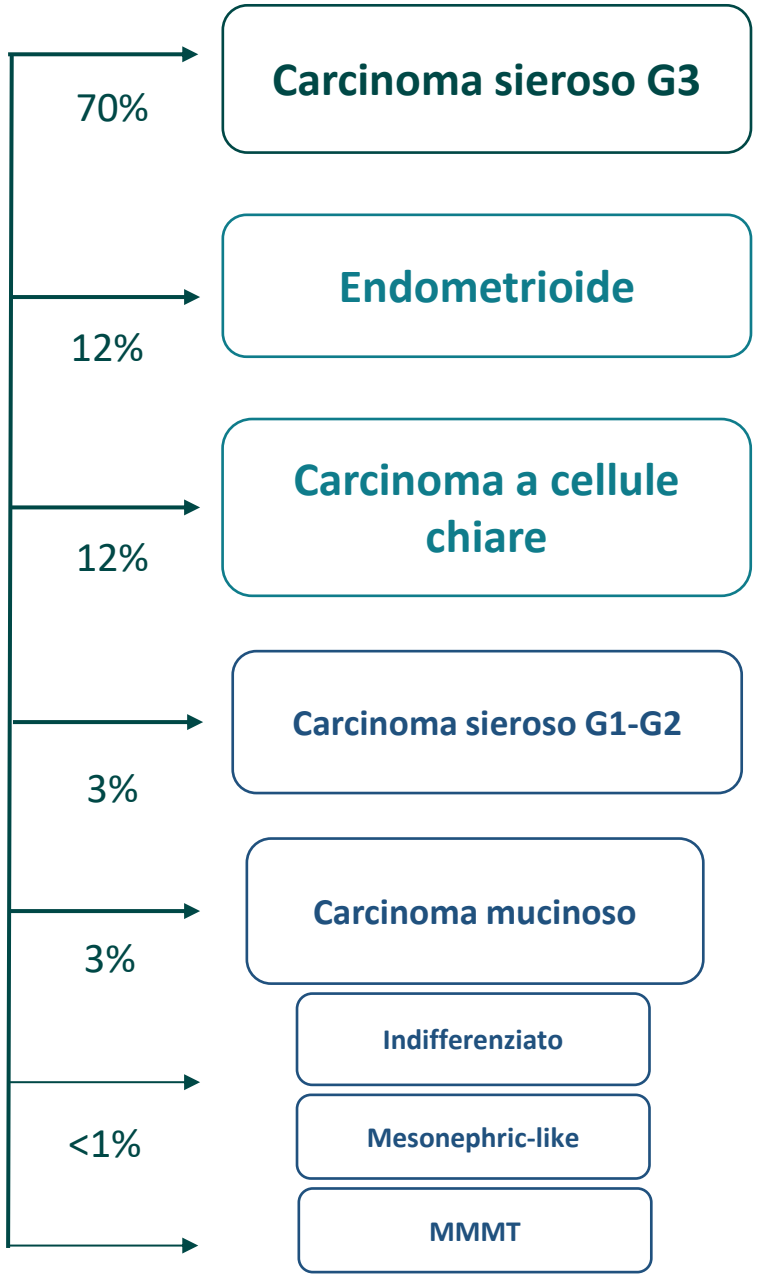
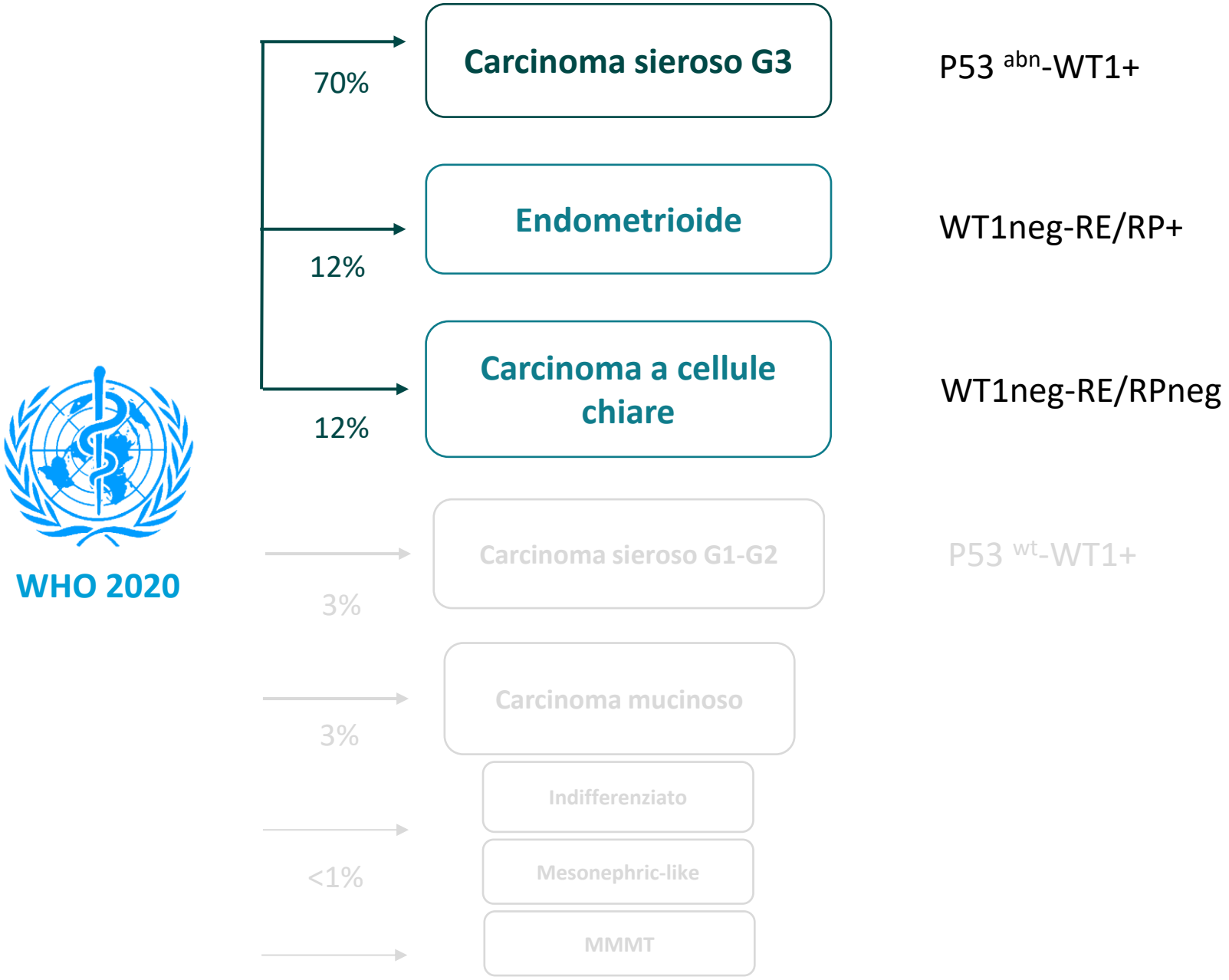
Non si parla di carcinoma ovarico ma di carcinomi ovarici ed è ora possibile sottoclassificare i carcinomi ovarici in sottogruppi riproducibili e clinicamente rilevanti

## Markers Immunoistochimici

WHO 2020



## Markers Immunoistochimici



Non si parla di carcinoma ovarico ma di carcinomi ovarici ed è ora possibile sottoclassificare i carcinomi ovarici in sottogruppi riproducibili e clinicamente rilevanti

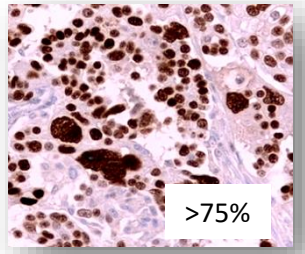
## Questi diversi gruppi differiscono rispetto a:

- ✓ fattori di rischio e precursori
- ✓ danni molecolari durante oncogenesi
- ✓ modalità di disseminazione
- ✓ risposta alla chemioterapia
- ✓ outcome

70%

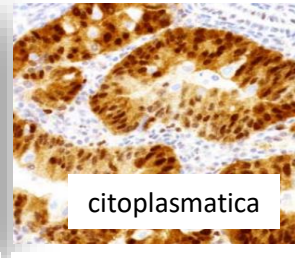
**Carcinoma sieroso G3**

P53 $^{abn}$-WT1+



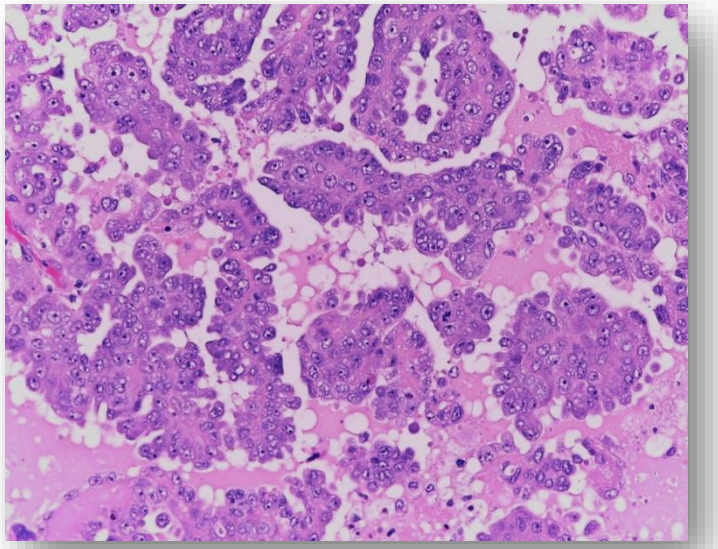

missense mutation

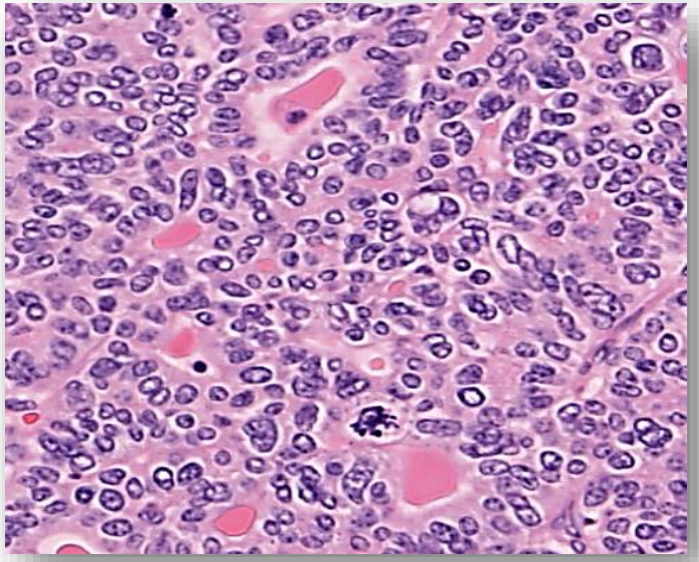

nonsense mutation

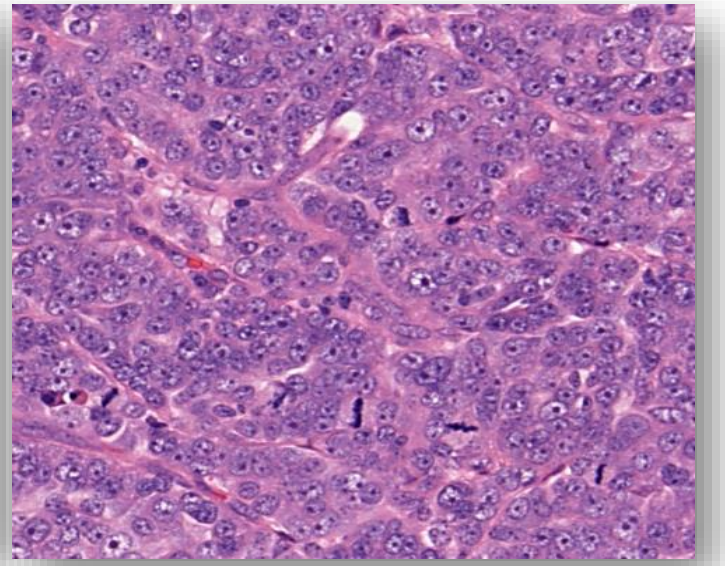



localizzazione proteina

WHO 2020







Morfologia SET (Solid pseudoEndometrioid Transitional)

BRCA 1/2 WT

BRCA 1/2 MUT

## Carcinomi ovarici associati ad endometriosi (40-90%)

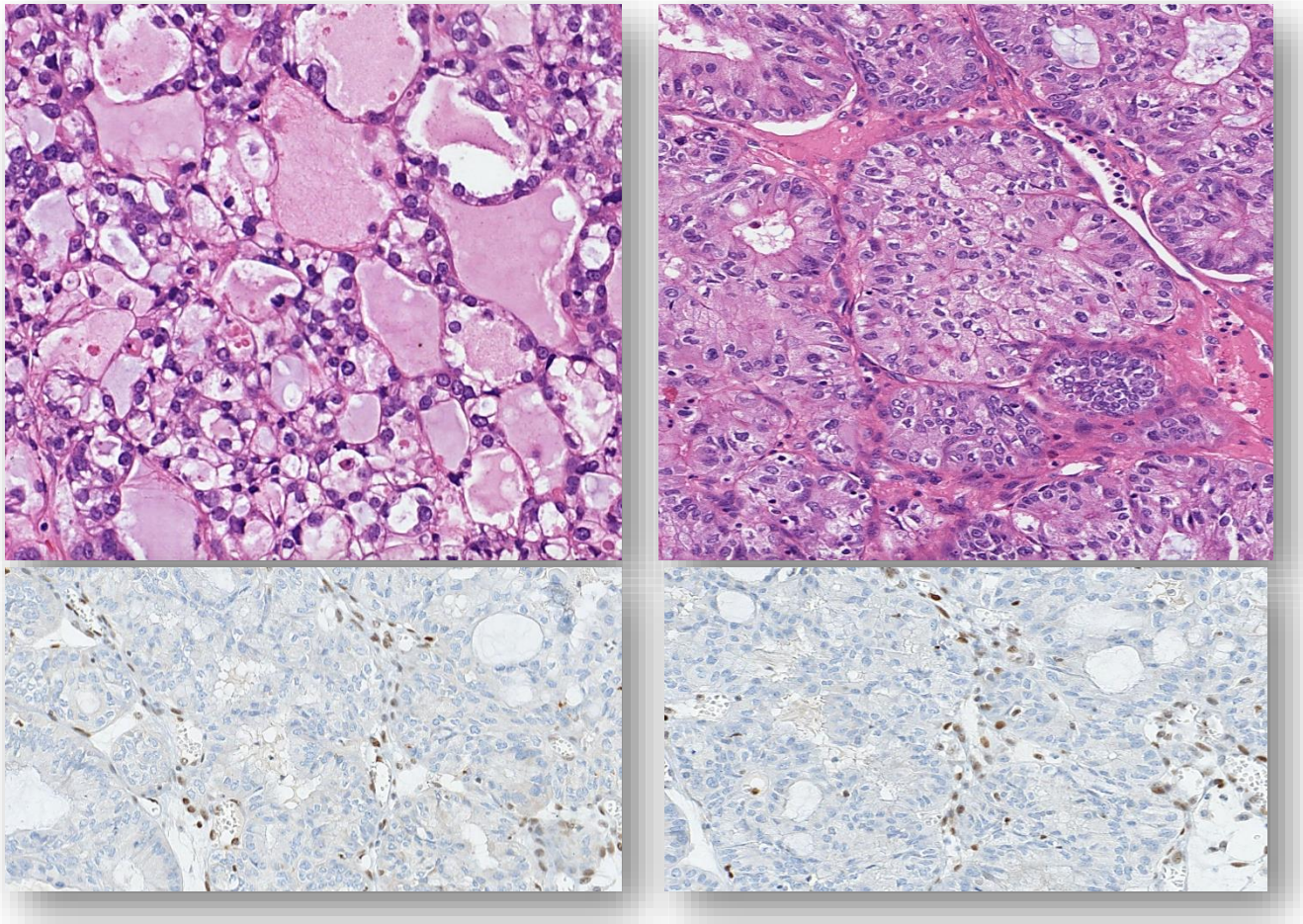
12% → **Endometrioide**

12% → **Carcinoma a cellule chiare**

1. Selezionare pts per counselling genetico
2. Immunoterapia

The Histomorphology of Lynch Syndrome–associated Ovarian Carcinomas

*Toward a Subtype-specific Screening Strategy*



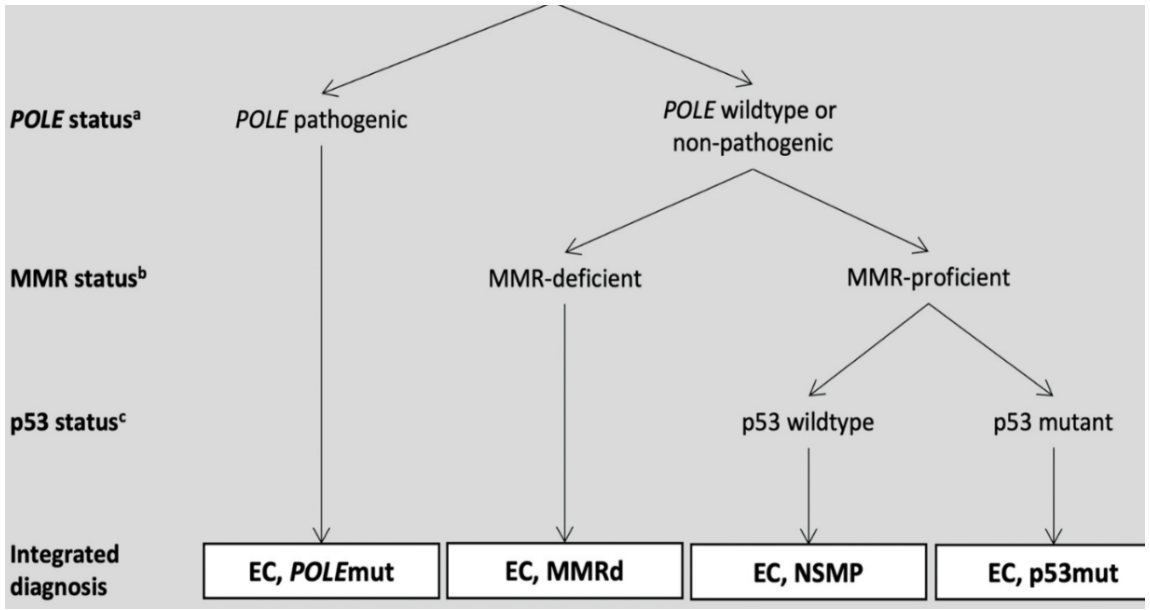
EOC INSTABILE per MSH2/MSH6

Carcinomi ovarici associati ad endometriosi (40-90%)

## Background morfologico e molecolare con EEC

12% → **Endometrioide**

12% → **Carcinoma a cellule chiare**




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

MODERN PATHOLOGY (2017) 30, 1748–1759

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]

**Endometrial Cancer Molecular Risk Stratification is Equally Prognostic for Endometrioid Ovarian Carcinoma**

Pauline Krämer*[1, 2], Aline Talhouk*[2, 3], Mary Anne Brett[4], Derek S Chiu[5, 3], Evan S Cairns[2], Daniëlla A Scheunhage[6], Rory FL Hammond[7], David Farnell[8, 3], Tayyebeh M Nazeran[8, 3], Marcel Grube[1], Zhouchunyang Xia[8, 3], Janine Senz[8, 3], Samuel Leung[8, 3], Lukas Feil[1, 2], Jana Pasternak[1], Katherine Dixon[9], Andreas Hartkopf[1], Bernhard Krämer[1], Sara Brucker[1], Florian Heitz[10, 11], Andreas du Bois[10], Philipp Harter[10], Felix KF Kommoss[12], Hans-Peter Sinn[12], Sabine Heublein[13], Friedrich Kommoss[14], Hans-Walter Vollert[15], Ranjit Manchanda[16, 17], Cornelis D de Kroon[18], Hans W Nijman[19], Marco de Bruyn[19], Emily F Thompson[8, 3], Ali Bashashati[3, 5, 8, 20], Jessica N McAlpine[2, 3], Naveena Singh[7], Anna V Tinker[21, 3], Annette Staebler[22], Tjalling Bosse[6], Stefan Kommoss[1], Martin Köbel[23], Michael S Anglesio[2, 3]

TCGA molecular classification in endometriosis-associated ovarian carcinomas: Novel data on clear cell carcinoma

Gynecologic Oncology 165 (2022) 577–584

Jonna Similä-Maarala[a], Piret Soovares[b], Annukka Pasanen[a], Terhi Ahvenainen[c,e], Pia Vahteristo[c,e], Ralf Bützow[a,1], Heini Lassus[d,*,1]

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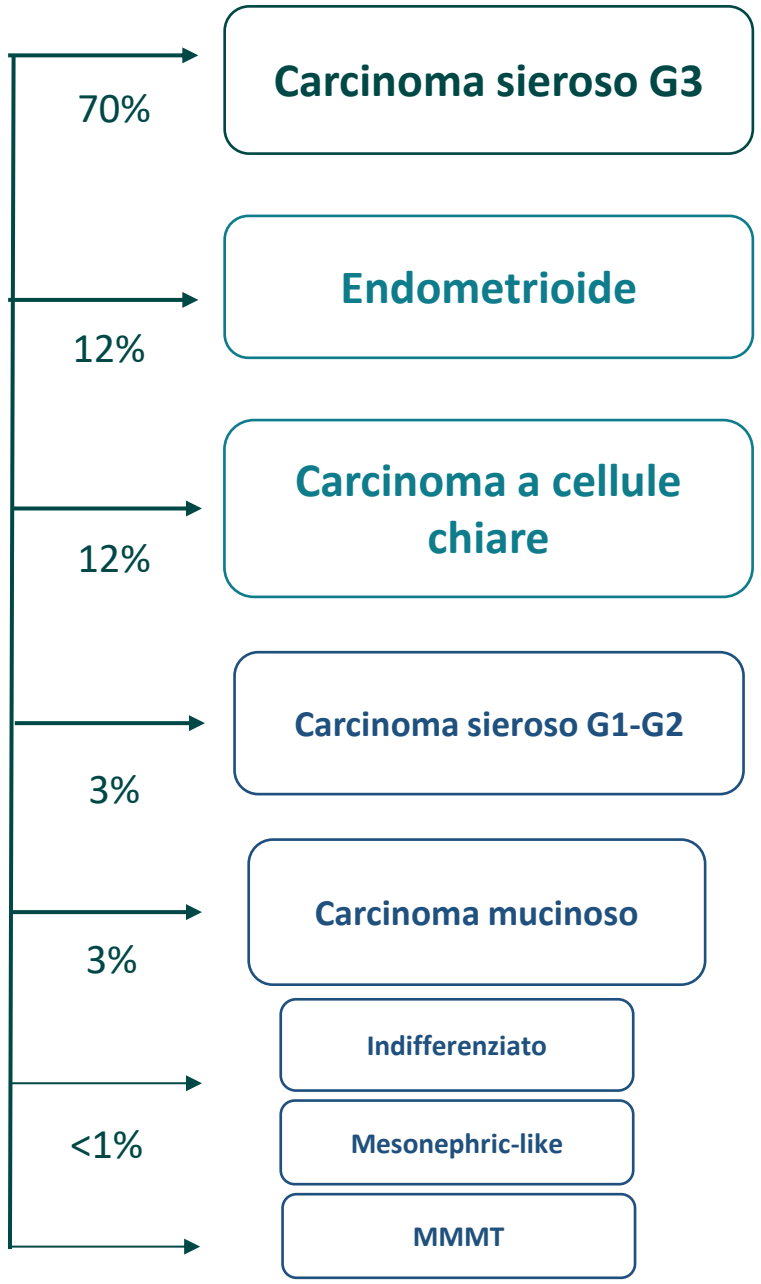
[d] Department of Obstetrics and Gynecology, Gynecologic Oncology, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 2, PO Box 140, 00029 HUS, Helsinki, Finland
[e] iCAN Digital Precision Cancer Medicine Flagship, Helsinki, Finland, University of Helsinki, Haartmaninkatu 8, PO Box 63, 00014, Finland




## Markers Immunoistochimici

P53 $^{abn}$-WT1+

WT1neg-RE/RP+

WT1neg-RE/RPneg

P53 $^{wt}$-WT1+

## Sottotipi molecolari

HRD-Dup, HRD-Del
……

POLE $^{mut}$ MMR$^{d}$
NSMP, p53 $^{abn}$

ARID1A, p53 $^{abn}$
ERBB2

p53 $^{abn}$, ERBB2

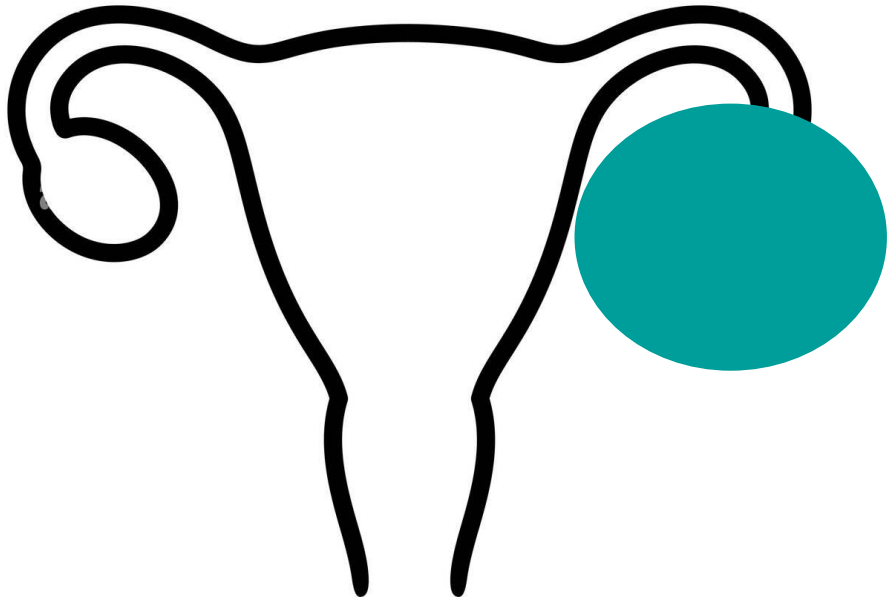
MMR$^{d}$

K-RAS

Correlazione tra morfologia ed outcome clinico può essere imperfetta nella medicina di precisione, necessario un approccio combinato che identifichi molecole predittive di risposta a terapie target

**MMR ICH e MSI test nei casi ambigui**

**HER2 test pan-cancer**



**Folato Receptor-α ICH**

**HRD e BRCA1/2 testing**

# Perché HER2 test?

**Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial**

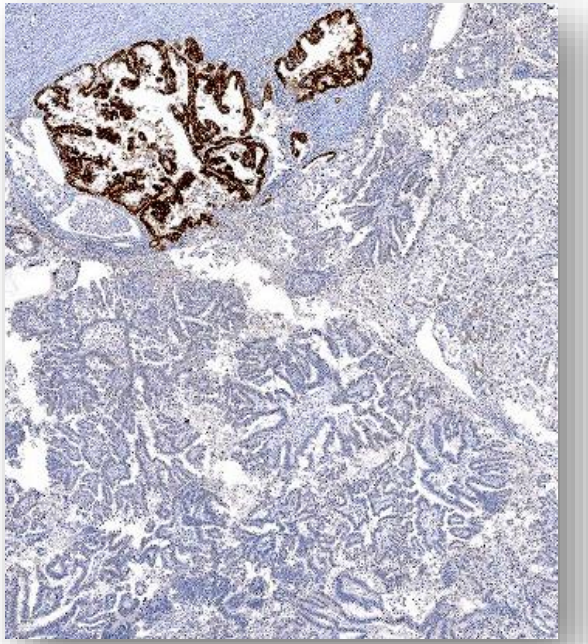
Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

| Overall response rate | | |
|---|---|---|
| | **All** | **IHC 3+** |
| Endometrial | 57.5% | 84.6% |
| Cervical | 50.0% | 75.0% |
| Ovarian | 45.0% | 63.6% |

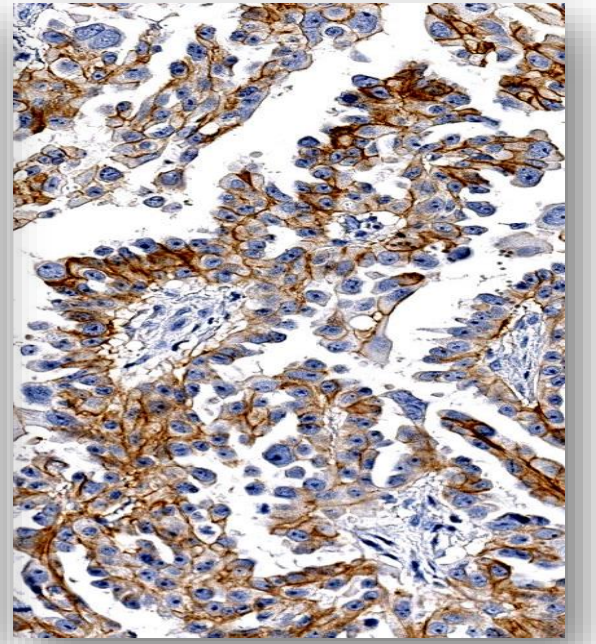
# Come testare HER2?

**Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice**

N Buza *et al* MODERN PATHOLOGY (2013) 26, 1605–1612



**Eterogeneità** IHC HER2



Espressione «**U-shaped**»

# Necessità di uno score «tessuto specifico»

| Current Criteria (Approved or Proposed) for HER2 Positivity by Immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH) in Different Tumor Types | | | | |
|---|---|---|---|---|
| | **Breast (ASCO/CAP 2018)[23]** | **Gastric (ASCO/CAP 2016)[36]** | **Colorectal (HERACLES Trial)[39]** | **Endometrial Serous (Fader et al Clinical Trial)[21]** |
| HER2 IHC 3+ | >10% circumferential, strong, complete | ≥10%, strong complete, or basolateral/lateral | ≥50% strong complete, or basolateral/lateral | >30% strong complete or basolateral/lateral |
| *HER2* FISH amplification | *HER2*/CEP17 ratio ≥2.0 and *HER2* signal ≥4.0 per nucleus OR ratio <2.0 and *HER2* signal ≥6.0 per nucleus (if IHC score 2+ or 3+) | *HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and *HER2* signal >6.0 per nucleus | *HER2*/CEP17 ratio ≥2.0 in ≥50% of cells | *HER2*/CEP17 ratio ≥2.0 |

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.

*HER2 Testing in Endometrial Serous Carcinoma*—Buza
Arch Pathol Lab Med—Vol 145, June 2021

# Folato Receptor-α (FR-α) ICH in HGSC

2025 approvazioni di Mirvetuximab soravtasina

## Come testiamo?

| |
|---|
| ≥ 75% tumour cells |
| Membranous staining, complete or partial |
| 2+ or 3+ intensity |
| Minimum 100 viable tumour cells |

# Sviluppo e validazione di score di risposta alla terapia adiuvante

| Chemotherapy Response Score (CRS) |
|---|
| CRS1 Nessuna o minima risposta tumorale. Cellule tumorali con nessuno a minime modificazioni regressive |
| CRS2 Risposta tumorale. Cellule tumorali facilmente identificabili e modificazioni regressive |
| CRS3 Risposta quasi completa o completa. Isolate cellule tumorali (<2 mm) |

Bohm et al. J Clin Oncol 33: 2457-2463 (2015)

Review Article

Pathological chemotherapy response score is prognostic in tubo-ovarian high-grade serous carcinoma: A systematic review and meta-analysis of individual patient data *The HGSC Collaborative Network*

P.A. Cohen et al. / Gynecologic Oncology 154 (2019) 441–448

1- CRS3 associato in modo significativo ad un miglioramento del PFS e OS rispetto a CRS1/2

2- Biomarker robusto e riproducibile

# Ruolo del patologo nell'era della medicina di precisione

1. Diagnosi di istotipo (morfologia non è obsoleta)
2. Fattori prognostici
3. Fattori predittivi di risposta a terapia
4. Selezione dei pazienti da inviare in consulenza genetica
5. Utilizzo di CRS come biomarcatore di risposta alla terapia neoadiuvante

# Grazie per l’attenzione !