XIX Congresso Nazionale A.G.E.O.

PREDITTIVITÀ E DIAGNOSI PRECOCE IN OSTETRICIA E GINECOLOGIA



Lettura magistrale

La battaglia contro il cancro e la medicina predittiva



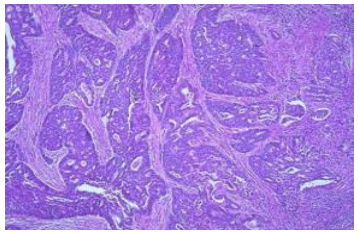
Fulvio Zullo

L'EVOLUZIONE DELL'APPROCCIO ALLA PAZIENTE

APPROCCIO INTEGRATO

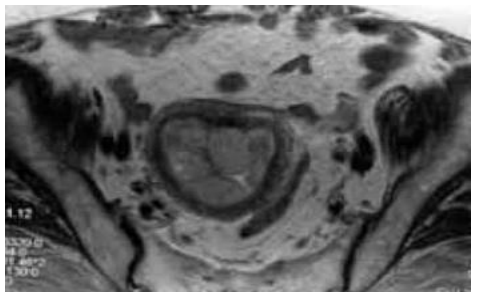


Anatomia Patologica



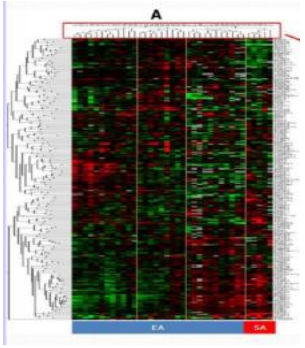
Ginecologia

Oncologia



PAZIENTE

Genetica



Radioterapia

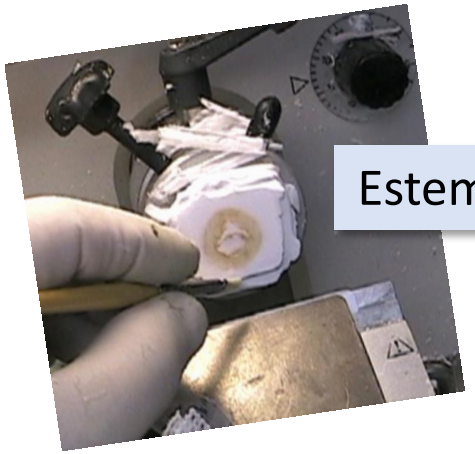
Medicina di laboratorio



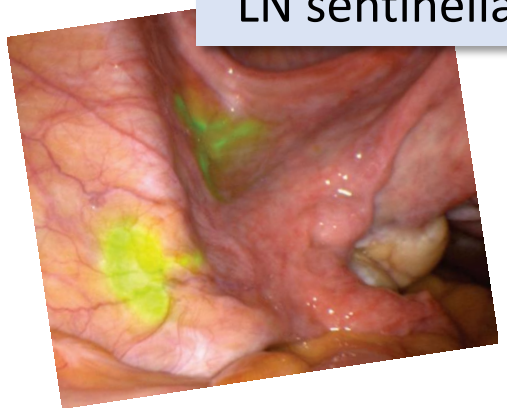
Diagnostica per immagini

L'EVOLUZIONE DELL'APPROCCIO ALLA PAZIENTE

Ieri, oggi e domani



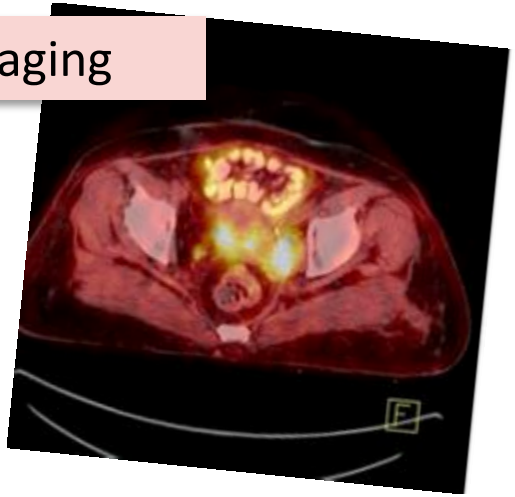
Estemporanea



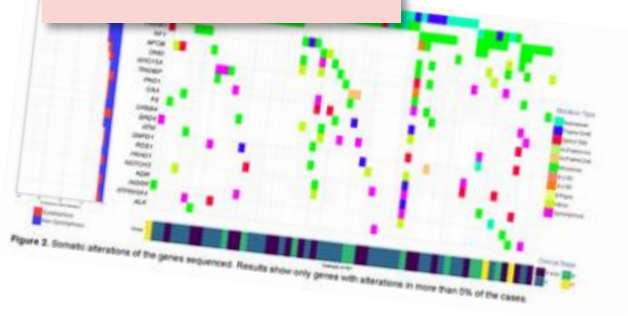
LN sentinella



Imaging



Profiling molecolare



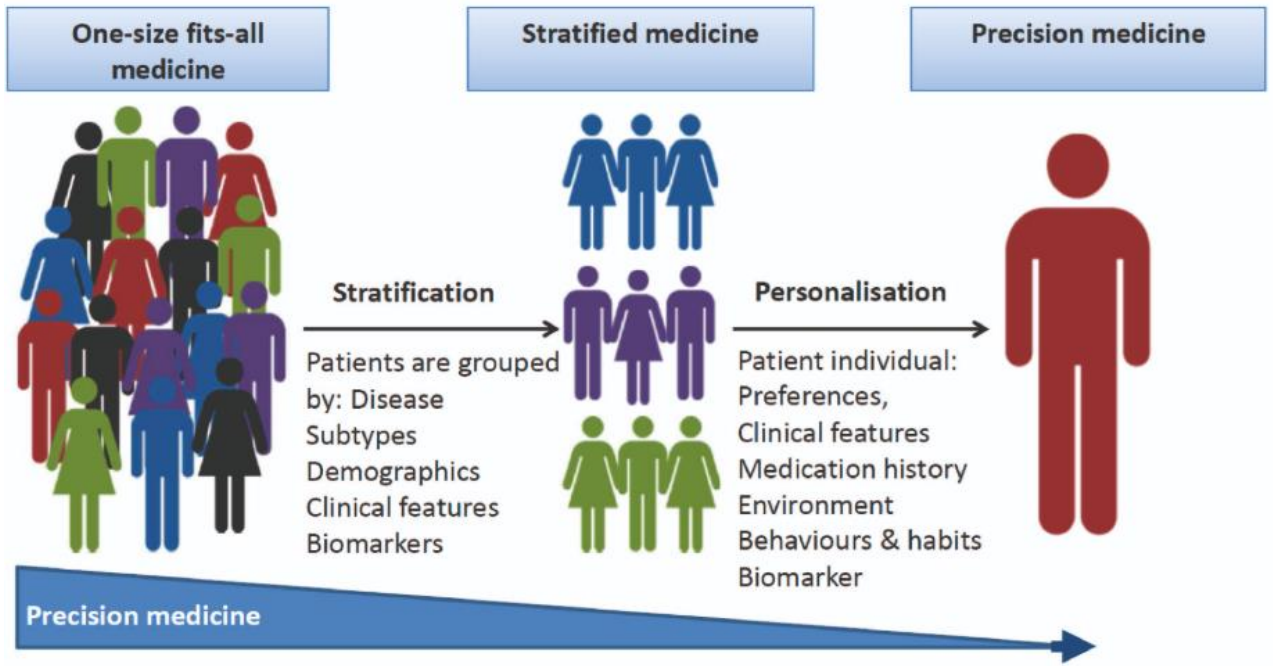
L'EVOLUZIONE DELL'APPROCCIO ALLA PAZIENTE

TAILORING

One-size fits-all medicine

Stratified medicine

Precision medicine



PRECISION MEDICINE

Gynecologic Oncology 141 (2016) 1

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Editorial

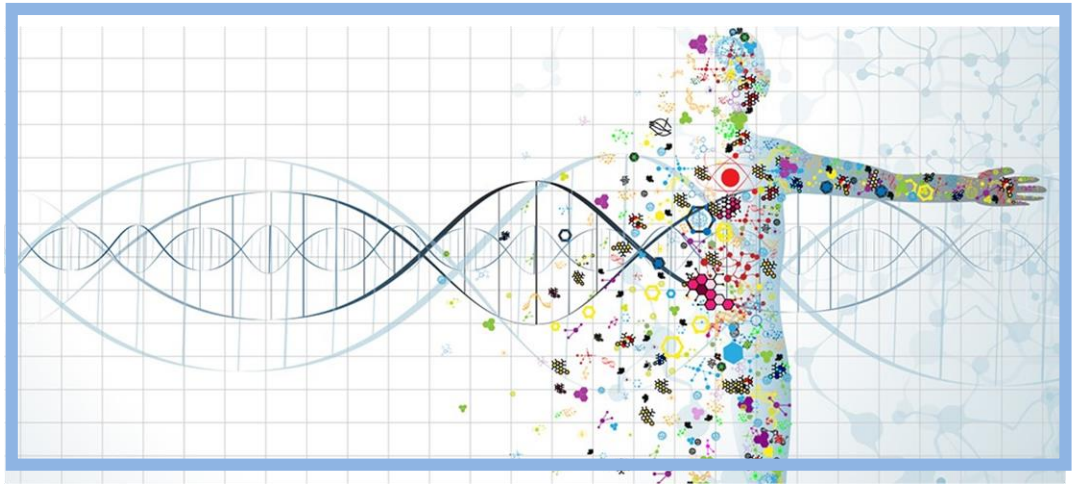
Precision medicine

La **Precision Medicine Initiative** è stata un'**area di interesse chiave** per il **National Cancer Institute** dal **2014 State of the Union address** del **Presidente Obama** (investiti **108 bilioni di dollari** nel solo 2016)

"the **right therapy**, at the **right time**, in the **right patient**..."

Quadri molecolari per **approcci innovativi**

Genomica, proteomica e trascrittomica del tumore per **prevenire, diagnosticare** o **trattare**



Misure preventive e terapeutiche **specificamente personalizzate al singolo individuo**

Una **core** o una **fine needle biopsy** ottengono materiale sufficiente per **analisi molecolari**. Anche tessuti archiviati (come i **blocchi in paraffina**) possono essere sequenziati senza problemi

Barroilhet, Gyn Onc 2018

Coleman, Gyn Onc 2016

ENDOMETRIAL CANCER (I)

Un caso emblematico

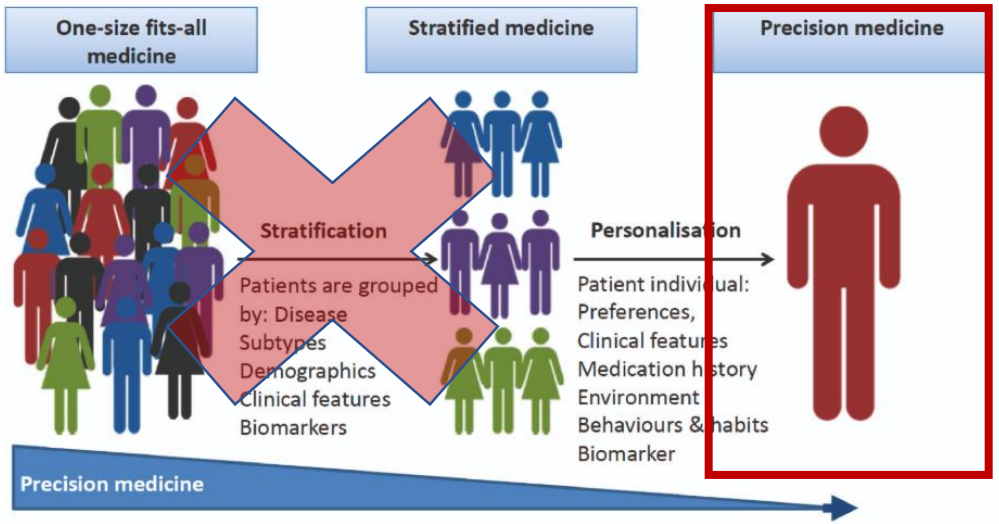
Tra il 1987 e il 2008 il **numero di donne con diagnosi di K endometrio è aumentato dell'80%** mentre il **numero di pazienti decedute è aumentato del 300%** circa

Mc Alpine, Cancer 2016

Trattamento con sola isterectomia



Fallimento della One-size fits-all medicine e della Stratified medicine?





ENDOMETRIAL CANCER (II)

MININVASIVITÀ

For many years, the surgical staging was **hysterectomy** conducted by a mid-line laparotomy **even in non referral center (increased mortality!)**. Nowadays, **total hysterectomy (with lymphadenectomy if necessary)** is **undoubtedly the gold standard approach**

In patients in cervical extension, **radical hysterectomy not necessary**: risk of parametrial involvement is minimal

Since the **1990s**, **laparoscopic surgery** was introduced into gynecological surgery, and soon implemented to treat patients with endometrial cancer. with benefits over laparotomy in terms of morbidity, recovery and long-term side-effects (no dissemination risks)

Recently, the assistance of **robots** to treat early endometrial cancers has become more popular. Of particular interest is the use of robotic surgery in **morbidly obese (BMI >50 kg/m2) patients** with endometrial cancer, which is reported to be a well tolerated and feasible option

FERTILITY-SPARING

Oral progestogens, **LNG-IUD** or **hysteroscopic resection +LNG/oral progestogen** for endometrioid, focal, G1, no ISLV, no myometrial or cervical invasion, as well as extrauterine metastases at MRI

NECESSITA' DI APPROCCIO INTEGRATO

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Uterine Neoplasm, Version 2.2017, April 26,2017.
Arend, Gyn Onc 2018
Ferguson, Gyn Onc 2018

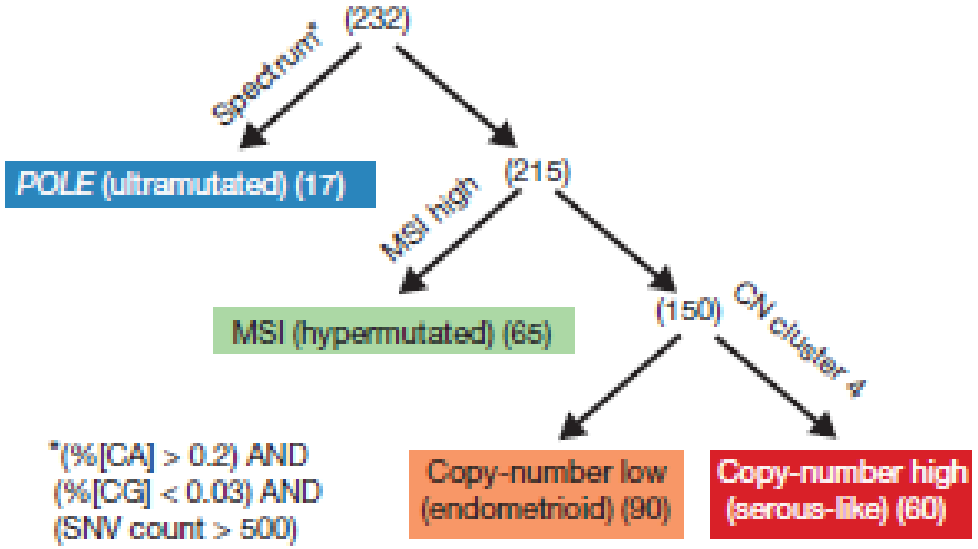
ENDOMETRIAL CANCER (III)

Una nuova classificazione

Il Cancer Genome Atlas (TCGA) Research Network ha recentemente implementato la classica classificazione anatomopatologica, **introducendo 4 gruppi diversi dal punti di vista molecolare e prognostico**

Pathological classification of endometrial carcinoma, WHO 2014.

Endometrioid carcinoma
Mucinous carcinoma
Serous endometrial intraepithelial carcinoma
Serous carcinoma
Clear cell carcinoma
Neuroendocrine Tumors
Mixed cell adenocarcinoma
Undifferentiated carcinoma
Dedifferentiated carcinoma



ATLAS The Cancer Genome Atlas Research Network, 2013

POLE-ultramutati caratterizzati da elevata mutagenicità e prognosi favorevole.

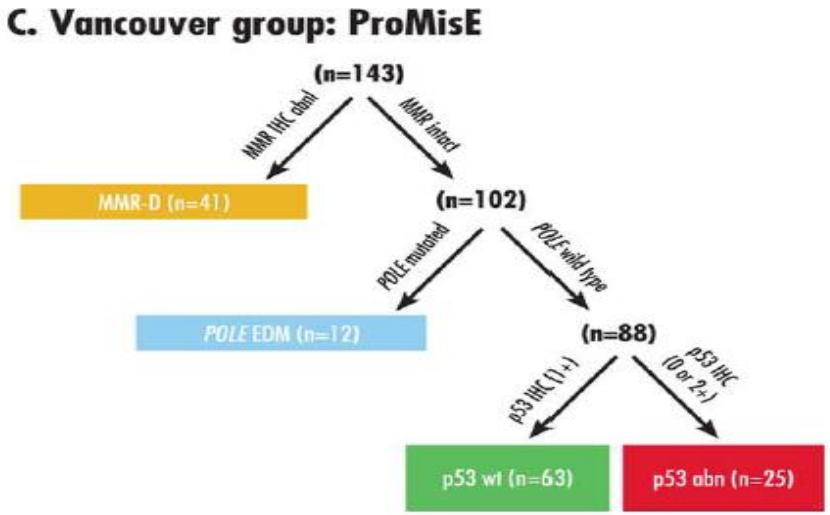
Associati ad alterazione del Mismatch Repair, instabilità dei microsatelliti e Sindrome di Lynch, potenzialmente responsivi ad immunoterapici di nuova generazione

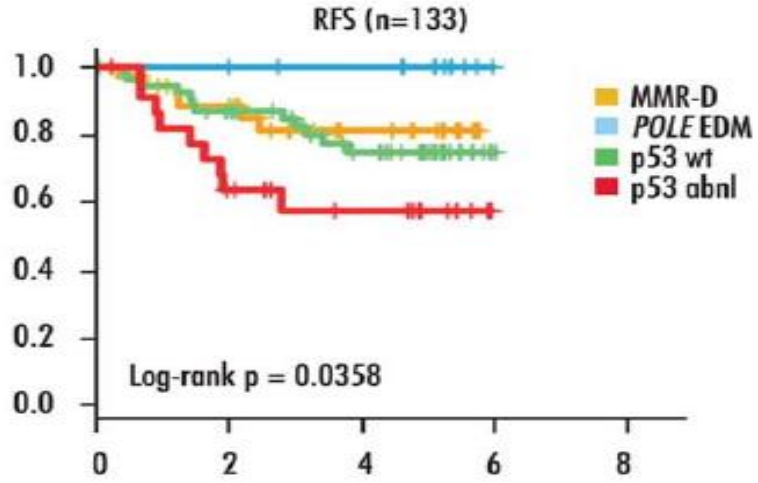
Generalmente endometrioidi G1-G2 caraterizzati da stabilità dei microsatelliti, bassa mutagenicità e mutazioni di CTNNB1 in circa la metà di casi.

Sierosi e 25% degli endometrioidi G3, caratterizzati da bassi livelli di ER/PR, frequenti mutazioni di TP53, FBXW7 e PPP2R1A, frequenti alterazioni CN, con outcome sfavorevole

ENDOMETRIAL CANCER (IV)

Dal profilo molecolare al trattamento





TOTAL of POSITIVE LNF: 8%

MMR-D → 8.3%

POLE-EDM→ 0%

P53 WT → 0%

P53 → 22.2 %

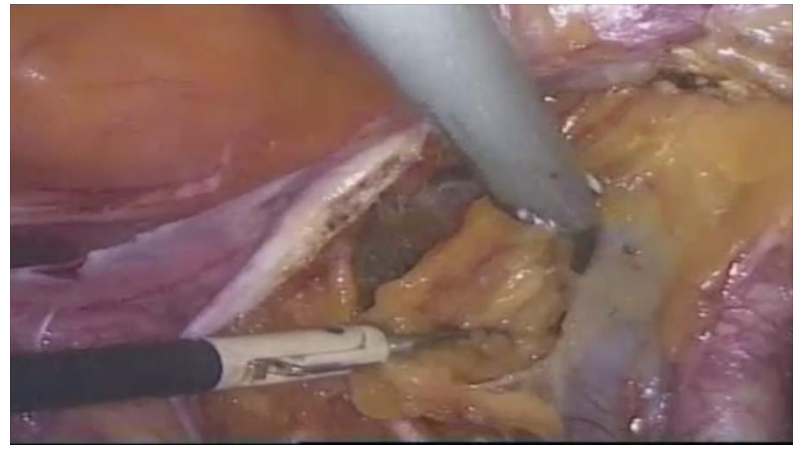
Actionability

McAlpine , Cancer 2016
Talhouk , Br. J Cancer 2015
Stelloo , Clin Cancer ReCancer s 2016

PEGGIOR PROGNOSI

CTNNB1-mutant/β1 catenin

L1CAM



ENDOMETRIAL CANCER (V)

Sottogruppi molecolari prognostici

ATLAS: un problema di applicabilità

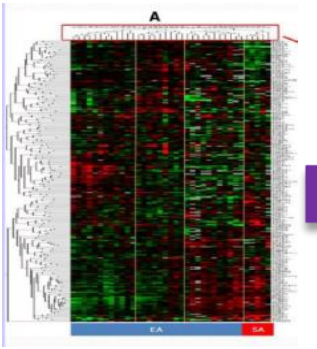
Analisi molecolare

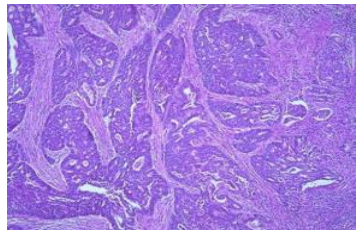


500 $ per campione



Necessità di surrogati più economici e tecnicamente più semplici da eseguire nella comune pratica clinica





Immunoistochimica come surrogato del sequenziamento molecolare

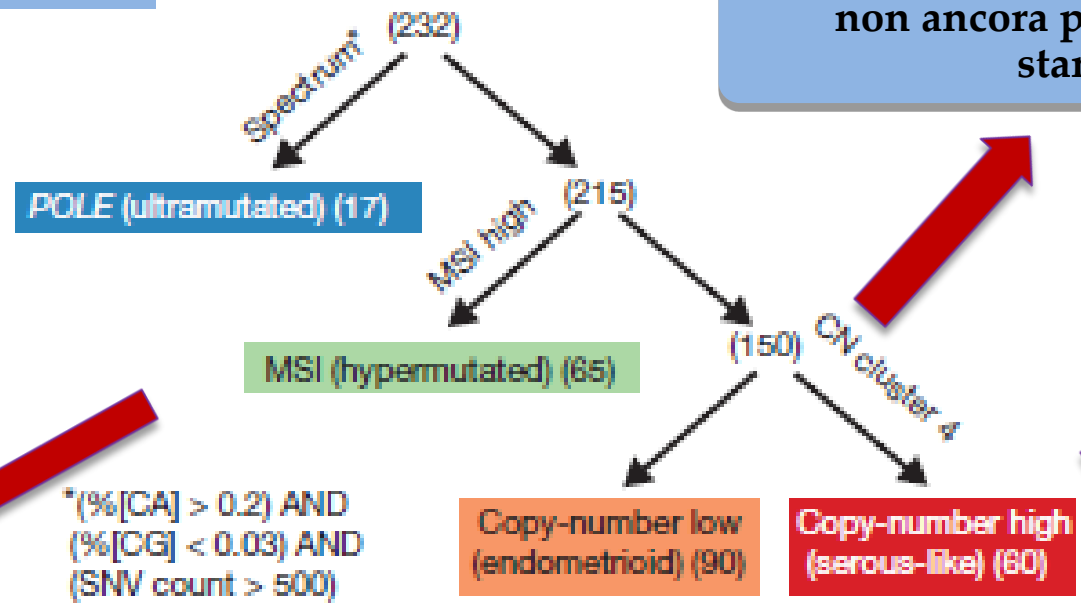
Valutazione accuratezza diagnostica e identificazione e standardizzazione di criteri interpretativi ottimali

ENDOMETRIAL CANCER (VI)

Valutazione e standardizzazione surrogati immunoistochimici: stato dell'arte

Mancante: globale caccia al tesoro

Criteri istologici associati
- ***Infiltrato linfocitario peritumorale***
- ***Associazione con perdita di PTEN***



Gruppo variegato da definire. Sottogruppo prognostico CTNNB1, IHC non ancora proposta e criteri non standardizzati

IHC p53 proposta, ma accuratezza diagnostica e criteri standardizzati mai definiti

IHC proposta, ma accuratezza diagnostica e criteri standardizzati mai definiti

Towards a widely applicable TCGA classification of endometrial cancer: diagnostic accuracy of p53 immunohistochemistry as surrogate of TP53 sequencing and optimal criteria to define p53 aberrant expression

Raffone A, Travaglino A, Saccone A, De Luca C, Mascolo M, Mollo A, De Placido G, Insabato L, Zullo F

Submitted to Cancer Metastasis Rev

L'**immunoistochimica per p53** è un **surrogato estremamente accurato** del **sequenziamento molecolare di TP53**. Una **forte espressione nucleare di p53 in ≥70-80% delle cellule tumorali** sembra il criterio ottimale per identificare le mutazioni di TP53.

Sens = 0.79
Spec = 0.96
DOR = 57,51
AUC = 0.99

Revisione risultati PROMISE per probabile miglioramento accuratezza dopo esclusione di casi con assenza di espressione di p53

ENDOMETRIAL CANCER (VII)

Valutazione e standardizzazione surrogati immunoistochimici: nuovi sviluppi

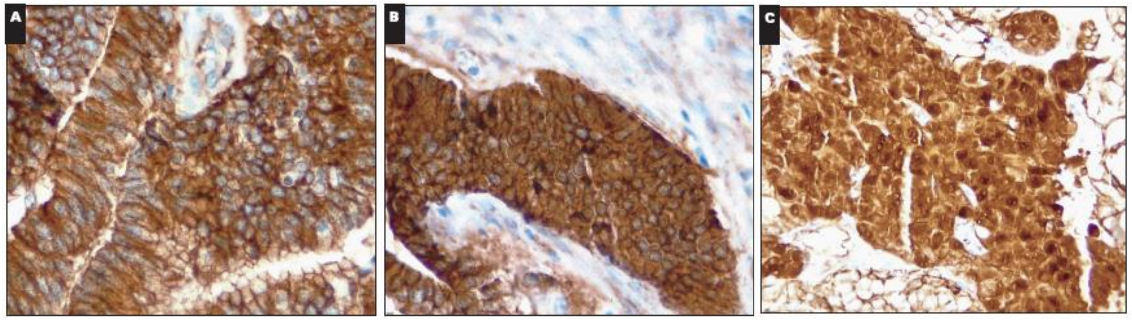
Immunohistochemical Nuclear Expression of β-Catenin as a Surrogate of *CTNNB1* Exon 3 Mutation in Endometrial Cancer

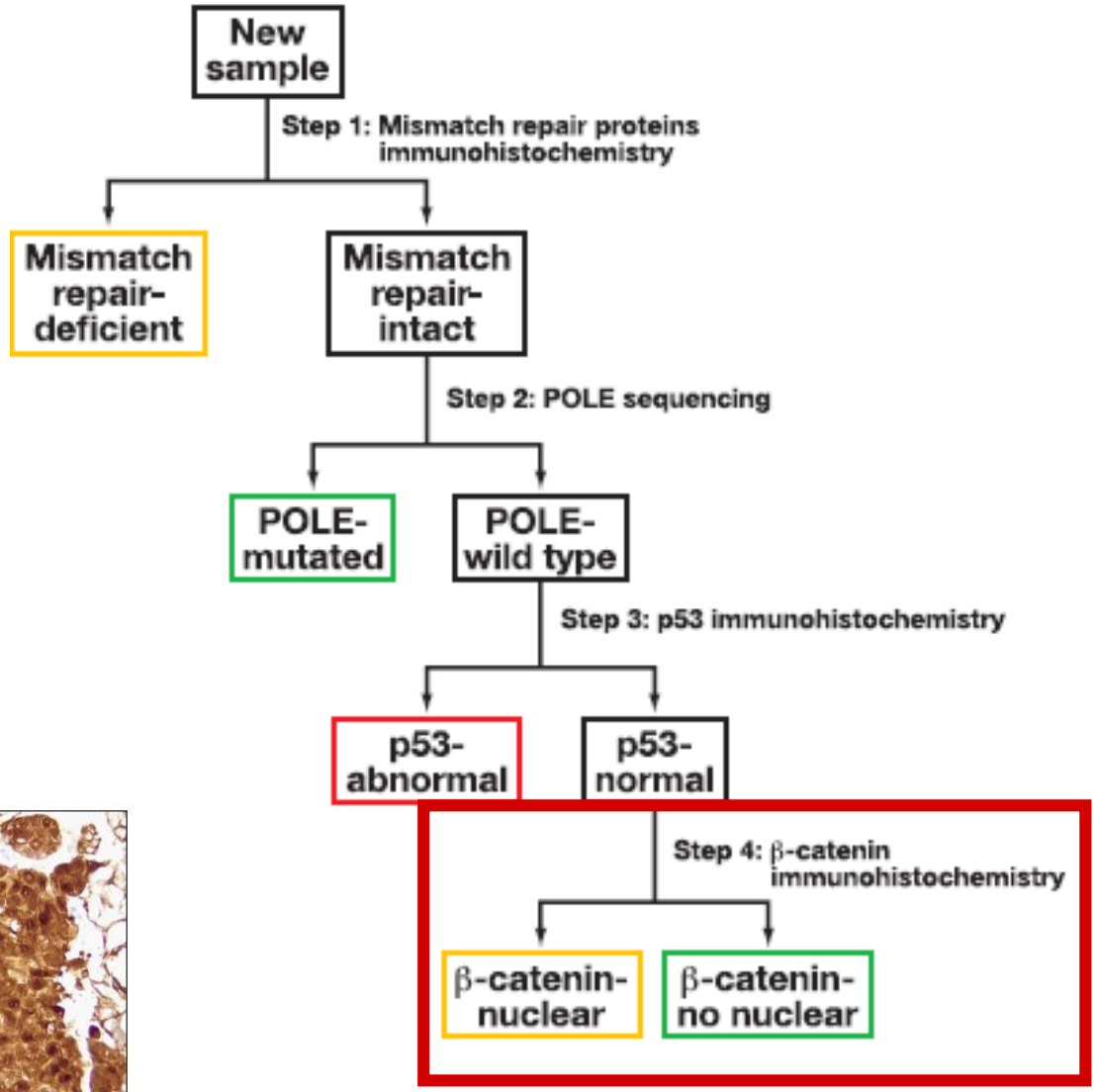
Antonio Travaglino, MD,[1] Antonio Raffone, MD,[2,o] Gabriele Saccone, MD,[2] Caterina De Luca, PhD,[3] Antonio Mollo, MD, PhD,[2] Massimo Mascolo, MD, PhD,[1] Giuseppe De Placido, MD, PhD,[2] Luigi Insabato, MD, PhD,[1] and Fulvio Zullo, MD, PhD[2]

Am J Clin Pathol 2019;XX:1-10

L'espressione nucleare di β-catenina è un accurato surrogato immunoistochimico delle mutazioni dell'esone 3 di CTNNB1 e potrebbe essere utilizzato come marcatore prognostico nella nuova stratificazione del rischio del cancro dell'endometrio

Sens = 0.88
Spec = 0.85
DOR = 27.16
AUC = 0.91





ENDOMETRIAL CANCER (VIII)

TCGA molecular groups of endometrial cancer: pooled data about prognosis

Raffone A, Travaglino A, Mascolo M, Guida M, Insabato L, Zullo F

Submitted to Cancer Metastasis Rev

Clinical trials are NOW necessary

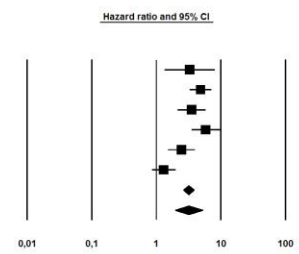
The **p53mt group** is consistently the group with the **worst prognosis**, with a **risk of death or progressive/recurrent disease** of **3-5-fold higher than that of the p53wt group**, and of **2-fold after adjusting for clinicopathological factors**. This indicates, on a hand, that **TP53 mutation** has a **strong and independent prognostic value**, on the other hand, that **other clinicopathological factors** still have their **role in worsening prognosis**.

The **MSI group** shows a **1.5-2-fold increased risk compared to the p53wt group**, which become n**on-significant after adjusting for clinicopathological factors**. Therefore, also **this group is affected by other prognostic factors**; however, the prognostic overlap with the p53wt group might be due to the heterogeneity of the latter one, supporting the **need for a further stratification of the p53wt group**. **CTNNB1 mutation** and its immunohistochemical surrogate (i.e. nuclear **β-catenin**) may be useful in this field.

The **POLEmt group** consistently shows **the most favorable prognosis**, and appears as **the group least affected by other clinicopathological factors**.

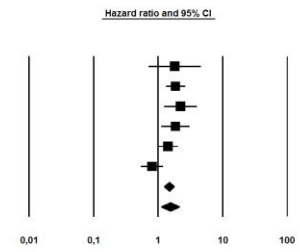
a

Model	Study name	Comparison	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	p53mt vs p53wt	3,290	1,349	8,024	2,618	0,009
	Stelloo 2016	p53mt vs p53wt	4,861	3,340	7,074	8,261	0,000
	Talhouk 2017	p53mt vs p53wt	3,540	2,163	5,794	5,029	0,000
	Kommoss 2018	p53mt vs p53wt	5,840	3,558	9,585	6,981	0,000
	Cosgrove 2018	p53mt vs p53wt	2,460	1,497	4,042	3,553	0,000
	Bosse 2018	p53mt vs p53wt	1,300	0,859	1,968	1,241	0,215
Fixed			3,147	2,591	3,823	11,553	0,000
Random			3,179	1,946	5,193	4,619	0,000



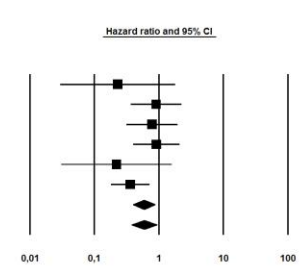
b

Model	Study name	Comparison	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	MSI vs p53wt	1,800	0,721	4,495	1,259	0,208
	Stelloo 2016	MSI vs p53wt	1,853	1,329	2,584	3,636	0,000
	Talhouk 2017	MSI vs p53wt	2,210	1,233	3,961	2,663	0,008
	Kommoss 2018	MSI vs p53wt	1,850	1,123	3,048	2,415	0,016
	Cosgrove 2018	MSI vs p53wt	1,410	0,970	2,050	1,800	0,072
	Bosse 2018	MSI vs p53wt	0,800	0,546	1,172	-1,146	0,252
Fixed			1,469	1,228	1,757	4,211	0,000
Random			1,522	1,101	2,104	2,541	0,011



c

Model	Study name	Comparison	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	POLEmt vs p53wt	0,230	0,030	1,767	-1,413	0,158
	Stelloo 2016	POLEmt vs p53wt	0,907	0,367	2,239	-0,212	0,832
	Talhouk 2017	POLEmt vs p53wt	0,780	0,315	1,931	-0,537	0,591
	Kommoss 2018	POLEmt vs p53wt	0,910	0,400	2,070	-0,225	0,822
	Cosgrove 2018	POLEmt vs p53wt	0,220	0,030	1,592	-1,500	0,134
	Bosse 2018	POLEmt vs p53wt	0,360	0,183	0,710	-2,949	0,003
Fixed			0,586	0,397	0,866	-2,686	0,007
Random			0,589	0,376	0,921	-2,320	0,020



OVARIAN CANCER (I)

PREVENTION: PROPHYLACTIC SALPINGECTOMY

Contents lists available at SciVerse ScienceDirect

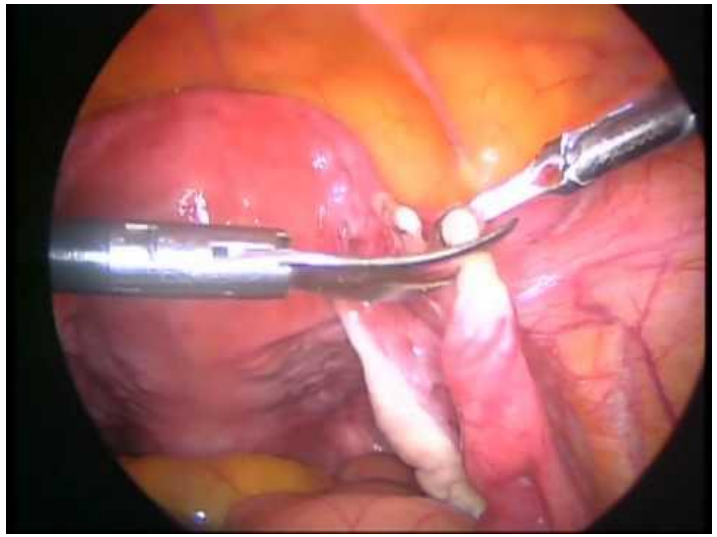
Gynecologic Oncology

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

Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: *Primum non nocere*

Michele Morelli, Roberta Venturella *, Rita Mocciaro, Annalisa Di Cello, Erika Rania, Daniela Lico, Pietro D'Alessandro, Fulvio Zullo

Department of Obstetrics & Gynecology, "Magna Graecia" University—Gynecologic Oncology Unit, "Tommaso Campanella" Cancer Center of Germaneto, Catanzaro, Italy



The **addition of bilateral salpingectomy to TLH** for **prevention of ovarian cancer** in women who do not carry a BRCA1/2 mutations **do not show negative effects on the ovarian function**. In addition, **no perioperative complications** are related to the salpingectomy step in TLH.

Prophylactic salpingectomy may be able **to reduce** the **incidence** of ovarian cancer **by 40% in 20 years**

OVARIAN CANCER (II)

TAILORED MANAGEMENT

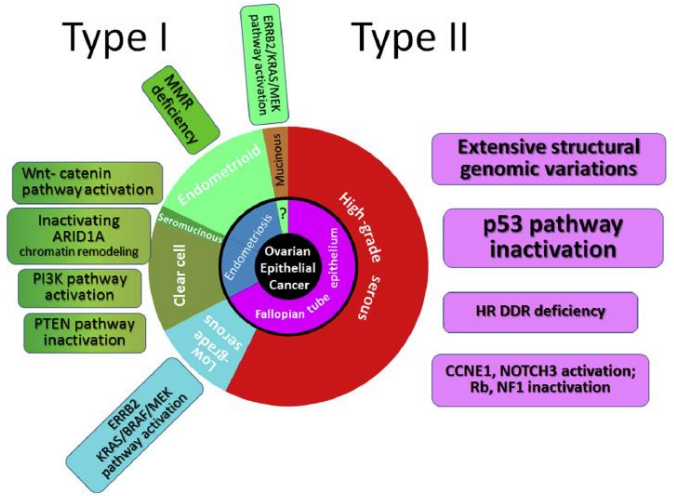
Mythology of optimal cytoreduction:
extreme cytoreduction led to **better prognosis**

The **retrospective** studies underlying this concept wrongly included **type I ovarian cancer** accoding to **Kurman classification**

Surgery should be **modulated by chemosensitivity** of each cancer

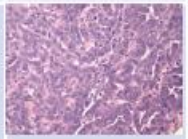
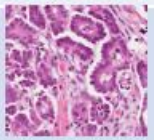
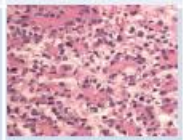
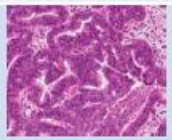
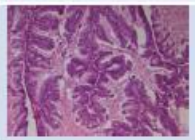
Type 1	Low chemosensitivity	Surgery is crucial
Type 2	High chemosensitivity	Surgery is not crucial

KURMAN TYPE	HISTOTYPE
Type I	Low grade serous, G1-G2 endometroid, mucinous, clear cell
Type II	High grade serous, malignant mixed mesoderms, undifferentiated



Kurman, Am J Pathol 2016
Levine, Gyn Onc 2018

Ovarian cancer (III)

	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
Pathology					
Molecular features	CNA high *TP53* *BRCA1/2* HRD	CNA low MAPK act. *KRAS* *BRAF*	*ARID1A* PI3K/AKT act. RTK/Ras act. MMR	*PI3KCA* *ARID1A* *KRAS* Wnt/β-catenin act. *PTEN*	*KRAS* *HER2* amplif.
Platinum Chemotherapy	Sensitive	Relatively Resistant	Relatively Resistant	Sensitive	Relatively Resistant
PARP inhibitor	Yes	-	-	Yes for high grade	-

	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Folate receptor	Yes	-	-	Yes	-
Hormone receptor	30% PR 80% ER	57% PR 87% ER	8% PR 19% ER	67% PR 76% ER	16% PR 20% ER
Hormonal therapy use	-	Yes	-	Yes	-
Mesothelin	50-80%		38%	?	10-30%
MMR deficiency	-	-	Yes	Yes	-
Anti-PD1	?	?	Yes	Yes	?

Lheureux, CA CANCER J CLIN, 2019

Ovarian cancer (IV)

	Epithelial ovarian cancer subtype	Approved treatment with Level I evidence	NCCN guidelines	Treatments in academic development
Incomplete surgery	HGSOC	Carboplatin/Paclitaxel Bevacizumab	Platinum-based chemo Bevacizumab concurrent and maintenance	PARP inhibitor Immunotherapy Folate receptor targeting
	HGSOC with BRCA1/2m	Carboplatin/Paclitaxel Bevacizumab Olaparib	Platinum-based chemo Bevacizumab concurrent and maintenance or Olaparib maintenance	Bevacizumab + PARP inhibitor Immunotherapy + PARP inhibitor
	LGSOC		Chemotherapy Hormonal therapy Bevacizumab	Letrozole *vs.* letrozole/chemo
	Clear cell		Platinum-based chemo Bevacizumab	Immunotherapy Radiation PARP inhibitor
	Endometrioid OC	Carboplatin/Paclitaxel Bevacizumab High grade endometrioid BRCAm: olaparib	Grade 1: Chemotherapy or Hormonal therapy Grade 2/3: Platinum-based chemo Bevacizumab or Olaparib maitenance for BRCA1/2m	Immunotherapy PARP inhibitor
	Mucinous		Platinum based Chemo + Bevacizumab or 5-FU+leucovorin+oxaliplatin+/-bevacizumab or capecitabine+oxaliplatin +/- bevacizumab	
Complete surgery No residual disease	HGSOC	Carboplatin/Paclitaxel Bevacizumab	Platinum-based chemo Bevacizumab concurrent and maintenance	Bevacizumab + PARP inhibitor Bevacizumab + PARP inhibitor + Immunotherapy Folate receptor targeting
	HGSOC with BRCA1/2m	Carboplatin/Paclitaxel Bevacizumab Olaparib	Platinum-based chemo Bevacizumab concurrent and maintenance or Olaparib maintenance	Bevacizumab + PARP inhibitor + Immunotherapy
	LGSOC		Chemotherapy Hormonal therapy	Letrozole *vs.* letrozole/chemo
	Clear cell		Platinum-based chemo Bevacizumab	
	Endometrioid OC	Carboplatin/Paclitaxel High grade endometrioid BRCAm: olaparib	Grade 1: Chemotherapy or Hormonal therapy Grade 2/3: Platinum-based chemo Bevacizumab or Olaparib maitenance for BRCA1/2 m	Immunotherapy
	Mucinous		Platinum based Chemo +/- Bevacizumab or 5-FU+leucovorin+oxaliplatin+/-bevacizumab or capecitabine+oxaliplatin +/- bevacizumab	
Early stage	HGSOC	Carboplatin/Paclitaxel	Platinum-based chemo	
	LGSOC		Stage IA/IB: Observe Stage IC: Observe or Platinum-based chemo or Hormone therapy	
	Clear cell		Stage IA: platinum-based chemo or Observe Stage IB/IC: Platinum-based chemo	
	Endometrioid OC	Carboplatin/Paclitaxel	Grade 1, Stage IA/IB: Observe Grade 1, Stage IC: Observe or Platinum-based chemo or Hormone therapy	
	Mucinous		Stage IA/IB: Observe Stage IC: Observe or Platinum-based chemo or 5-FU+leucovorin+oxalplatin or Capecitabine+oxalplatin	

Lheureux, CA CANCER J CLIN, 2019

OVARIAN CANCER (V)

TAILORED MANAGEMENT BASATO SU UNA TAILORED DIAGNOSI

L'espressione immunoistochimica di più di 500 proteine è risultata statisticamente differente tra endometrioidi e sierosi di alto grado (n= 361)

Nuovo pannello immunistochimico a 8 markers per differenziare l'istotipo endometrioide dal sieroso di alto grado

Markers attualmente raccomandati

KIAA1324,
SCGB2A1,
MUC5B,
PLCB1,
PAM,
CTNNB1,
WT1
TP53

Tasso di corretta classificazione di sierosi di alto grado migliora dal 90.7% (standard attuale con I soli WT1+ p53) al 99.2% col nuovo pannello a 8 markers

KIAA1324 è il marker più associato a istotipo endometrioide

PLCB1, KIAA1324, e SCGB2A1 anche significativamente associate a prognosi favorevole all'interno dell'istotipo endometrioide suggerendo eterogenità biologica all'interno di questo istotipo

Riduzione del rischio di undertreatment di pazienti con istotipo sieroso di alto grado, aumentando l'elegibilità a terapie mirate (PARP-inibitori) e inidrizzando ad appropriati programmi di screening ereditari (BRCA1/2, syndrome di Lynch).

Dieters-Castator et al. Clin Cancer Res. 2019

OVARIAN CANCER (VI)

HIGH GRADE SEROUS HISTOTYPE MOLECULAR SUBSTRAFICATION

High grade serous histology has been demonstrated to harbor **defective homologous recombination** pathways in approximately **50%** of cancers related to several mechanisms, including germline and somatic BRCA mutations, epigenetic inactivation of BRCA, and abnormalities of other DNA repair genes

The **TCGA** has classify **high grade serous** into four **molecular subtypes**: **mesenchymal, proliferative, differentiated, or immunoreactive.**

The **immunoreactive subtype** has been associated with a **better prognosis** and the **mesenchymal subtype** has been associated with **worse prognosis**

The **mesenchymal subtype** has also been associated with **response to bevacizumab** treatment

Patients with **mesenchymal subtype** had a **higher rate of upper abdominal or miliary disease**, a **lower rate of complete gross resection** , and a **worse overall suvival**.

The **mesenchymal subtype** could be a useful **preoperative biomarker** to indicate which patients have a **low likelihood to benefit from prmary cytoreductive surgery**

The Cancer Genome Atlas Research Network, Nature 2011

Levine, Gyn Onc 2018

OVARIAN CANCER (VII)

MUCINOUS HISTOTYPE MOLECULAR SUBSTRAFICATION

Mucinous ovarian cancers are not associated with *BRCA* mutations or defects in homologous recombination, making them unlikely to benefit from PARP inhibitors.

The most frequent alterations are *KRAS* mutations (40-65%), *c-MYC* amplifications (65%), *HER2* amplifications (20-38%), and *TP53* mutations (50-75%). Other alterations have been identified at lower frequencies, such as homozygous deletions in *CDKN2A/B* (25%), mutations in *PI3KCA* (13%), and mutations in *PTEN*, *BRAF*, *FGFR*, *KIT*, or *STK11* (2-5%).

These genomic profiling studies allow mucinous ovarian cancers to be grouped into therapeutically relevant subsets

***KRAS* mutations and *HER2* amplifications tend to be mutually exclusive. The subset of HER2– positive tumors with wild-type *KRAS* may be particularly suited to HER2-directed therapies such as trastuzumab.**

EGFR amplification or mutations in *BRAF*, *FGFR*, or *STK11* have been detected in *HER2*-negative tumors with wild-type *KRAS*, suggesting that these tumors may be responsive to inhibitors of EGFR, BRAF, FGFR2, or mTOR, respectively.

The absence of a *KRAS* mutation identifies a subset of patients with colorectal cancer who are more likely to benefit from the EGFR-inhibiting antibody, cetuximab

Most mutations in the PI3K pathway occur with a *KRAS* mutation, and preclinical studies have shown synergy between MEK and PI3K inhibition in mucinous ovarian cancer cell lines with *KRAS* mutations.

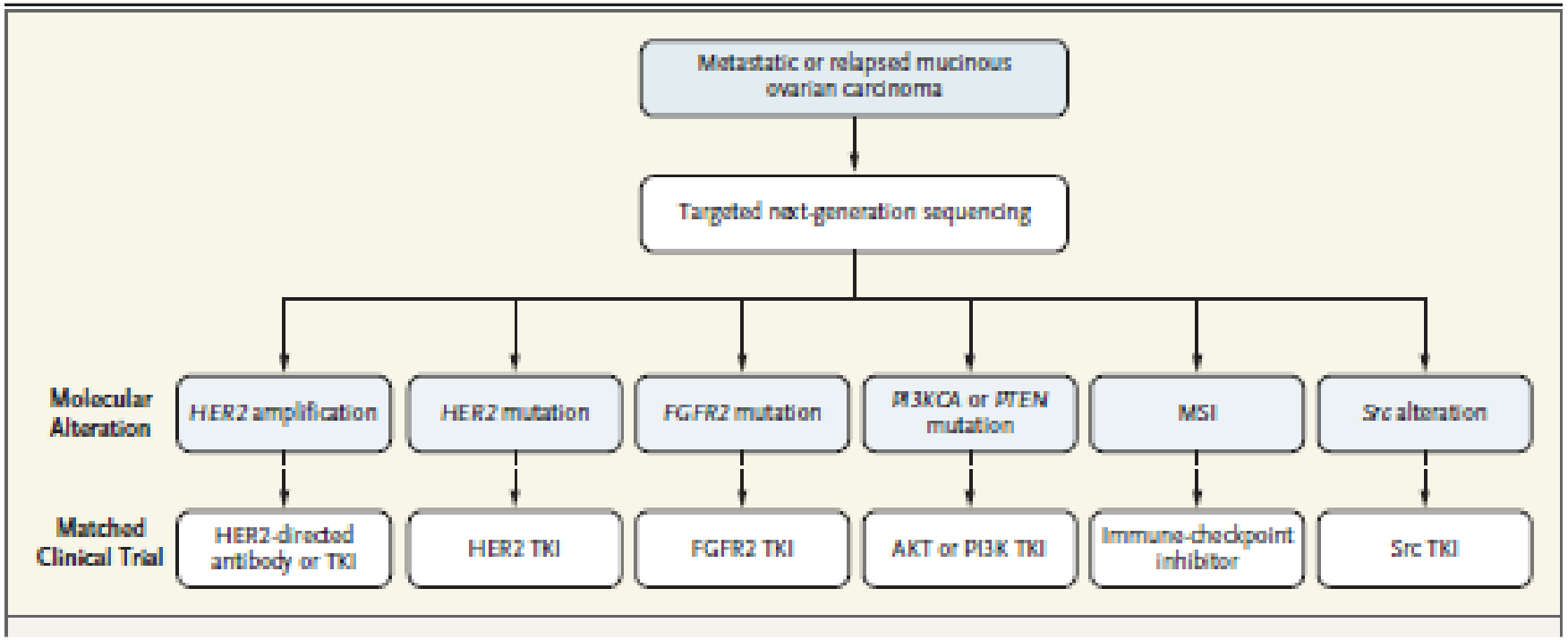
Morice. N Engl J Med. 2019

OVARIAN CANCER (VIII)

MUCINOUS HISTOTYPE MOLECULAR SUBSTRAFICATION

TP53 mutations are detected at a remarkably high frequency in mucinous ovarian cancer (in 50 to 75% of cases). APR-246 is a small molecule designed to restore wild-type p53 function, whereas the WEE1 inhibitor, AZD1775, abrogates the G2-M cell-cycle checkpoint, selectively sensitizing p53-deficient cells to DNA-damaging agents. Both agents are being investigated in clinical trials of *TP53*-mutated tumors.

Defects in the mismatch-repair pathway of DNA repair that result in a tumor with microsatellite instability have been detected in 15 to 20% of patients with mucinous ovarian cancer. Given that tumors with microsatellite instability have high mutation burdens and dense immune infiltrates that are characteristic of other tumor types that respond to immunecheckpoint inhibition, enthusiasm is high for testing inhibitors of PD-1 (programmed death 1) or PD-L1 (programmed death ligand 1) in such subset



Morice. N Engl J Med. 2019

OVARIAN CANCER (IX)

Circulating cell-free DNA and circulating tumor cells, the "liquid biopsies" in ovarian cancer

Cheng *et al. Journal of Ovarian Research* (2017) 10:75
DOI 10.1186/s13048-017-0369-5

PROSPETTIVE FUTURE

L'applicazione della caratterizzazione molecolare di cfDNA, CTC, cell-free microRNAs ed esosomi (**BIOPSIA LIQUIDA**) migliora la previsione di risposta a terapie mirate, e permette **l'identificazione di sottopopolazioni con specifici *signature* genici**, consentendo non solo la **diagnosi** precoce, ma anche la **stratificazione** della indicazione terapeutica.

Muinelo-Romay Int J Mol Sci. 2018
Giannopoulou, *Transl Res* 2019

✓Lo studio su **liquido ascitico** potrebbe consentire di identificare il **profiling molecolare delle cellule tumorali.**
✓È stato osservato su cellule di liquido ascitico come elevati livelli di **p70S6K** (indotti da **PI3K**) correlano con maggiore **CHEMIO-RESISTENZA.** Cellule di liquido ascitico che tendono a formare **SFEROIDI** sono significativamente correlate a RICORRENZA DI MALATTIA. Elevati livelli di **VEGF-A** e **IL-6,8,10** nel liquido ascitico sono correlati ad un minore tempo di progressione di malattia (**progression free survival**).

✓Identificare le pazienti che non risponderanno alla Chemioterapia e per le quali è meglio la Chirurgia Up-front

✓Identificare pazienti che dopo NACT potrebbero evitare la LND (*la LND pelvica e para-aortica durante la chirurgia di intervallo potrebbe essere omessa, almeno nell'HGSC, poichè non associata ad aumento della sopravvivenza*) ***Fagotti Ann Surg Oncol 2012; Shawrtz ., Anticancer Res 2015***

✓Il LNF sentinella potrebbe potenzialmente evitare la LND negli stadi iniziali del cancro ovarico ***Kimming ., JCO 2017***

OVARIAN CANCER (X)

PROSPETTIVE FUTURE

TIL-based ACT

Adoptive cell transfer (ACT) based on autologous T cells derived from tumorinfiltrating lymphocytes (TILs). TIL-based ACT is a highly personalized cancer treatment. T cells are harvested from autologous fresh tumor tissues, and after ex vivo activation and extensive expansion, are reinfused to patients.

TIL-based therapies have only been offered in small phase I/II studies in a few centers given the highly specialized care required, the complexity of TIL production and the very intensive nature of the three-step treatment protocol.

The treatment includes high-dose lymphodepleting chemotherapy, the infusion of the expanded and activated T cells and interleukin-2 (IL-2) injections to increase survival of the T cells. TIL-based ACT has been used to successfully treat a few patients with ovarian and cervical cancer. Several TIL-based ACT trials are actively recruiting patients with gynecologic malignancies.

Mayor, Gynecol Oncol 2018

BRCA status

Lo stato BRCA potrebbe essere utile per personalizzare il trattamento in pazienti con recidiva di carcinoma ovarico sieroso di alto grado, dal momento che pazienti BRCmt mostrano la migliore sopravvivenza post-recidiva (PRS) indipendentemente dalla citoriduzione secondaria con una PRS di 73% in donne non citoridotte e del 78% in quelle citoridotte (p=0,558). D'altra parte, pazienti BRCAwt sottoposte a citoriduzione secondaria avevano una PRS significativamente più alta comparata a quelle che non la ricevevano (5-year PRS of 54% vs. 42%; p = 0.048).

Marchetti, Ann Surg Oncol, 2018

Angiogenesis-related gene expression profile

Five genes [angiopoietin 1 (ANGPT1), aryl hydrocarbon receptor nuclear translocator (ARNT), CD34, epidermal growth factor (EGF) and matrix metallopeptidase 3 (MMP3)] as being statistically associated with response to treatment in high grade serous ovarian cancer (HGSOC).

Seven genes [angiotensinogen (AGT), CD34, EGF, erythropoietin receptor (EPOR), interleukin 8 (IL8), MMP3 and MMP7)] showed an AUC of 0.679 in predicting the response to treatment.

An angiogenesis-related gene expression profile useful for response prediction in HGSOC was identified, supporting the important role of angiogenesis in HGSOC.

Mendiola, Anticancer Res. 2018

CERVICAL CANCER (I)

Spread of **invasive treatment**, including **pelvic exenteration** following Halsted theory

Increasing consideration is being given to **complications of radical surgery**, the potential long-term effects and the ultimate impact on the patient's **quality of life**, including **lymphedema**, **changes of body image and sexuality**, **fistula**, **pyelonephritis**, **necrosis**

Chemoradiation as effective as radical hysterectomy

On the other end of the surgical spectrum, **fertility sparing** has become a **more common request** and a challenging field for surgeons. However, fertility sparing approach has been associated with very **poor obstetric outcomes**

Identification of **preoperative MRI criteria** (e.g. tumour size cut off and parametrial involvement) to accurately **select patients for less radical surgery**

Dilley Gyn Onc 2018
Trimble Gyn Onc 2018

CERVICAL CANCER (II)

BATTUTA D'ARRESTO PER L'APPROCCIO LAPAROSCOPICO IN ONCOLOGIA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

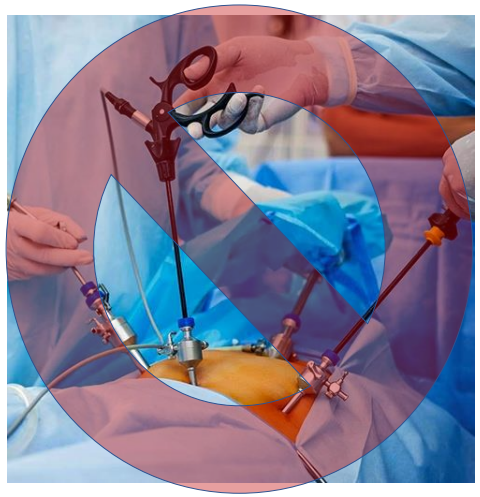
Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

Cervical cancer - Stages IA1 to IB1

Laparoscopic/Robotic (MIS) vs open radical hysterectomy (TARH)

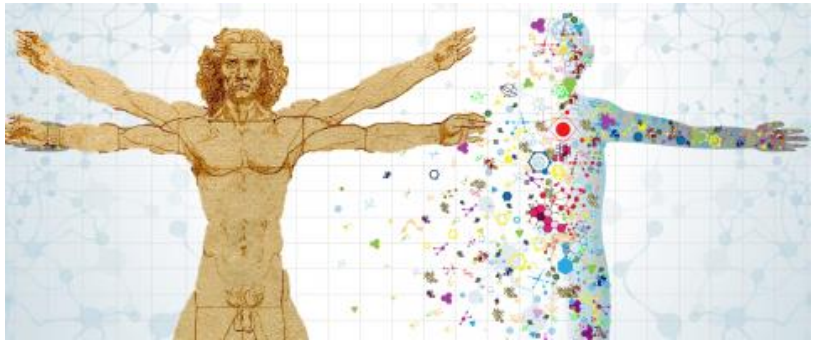
312 women randomized to **TARH** vs **319** to **MIS** (84% laparoscopy, 16% robotic)
92% Stage IB1
DFS 4,5 year rate: 86% MIS vs **96,5% TARH −10.6 percentage points** (95% CI, −16.4 to −4.7)
DFS 3-year rate: 91.2% MIS vs**. 97.1% TARH**
HR for disease recurrence or death from cervical cancer: 3.74 (95% CI, 1.63 to 8.58)
OS 3-year rate: 93.8% MIS vs. **99.0% TARH**
HR for death from any cause: 6.00 (95% CI, 1.77 to 20.30)



MIS associated with higher recurrence rates and worse overall survival

CERVICAL CANCER (III)

TCGA FEEDBACK



Oncogenic mutations in cervical cancer include **PIK3CA** and **EGFR**

KRAS mutations are seen mostly commonly in **adenocarcinomas**

Amplifications in immune targets CD274 (also known as **PD-L1**) and PDCD1LG2 (also known as **PD-L2**), and the **BCAR4 long non-coding RNA** has been associated with **response to lapatinib**.

Unique set of **endometrial-like cervical cancers**, comprised predominantly of **HPV-negative tumours** with relatively high frequencies of **KRAS**, **ARID1A** and **PTEN** mutations

Integrative clustering of 178 samples identified **keratin-low squamous**, **keratin-high squamous** and **adenocarcinoma-rich subgroups**

The Cancer Genome Atlas Research Network, Nature 2017

ENDOCERVICAL CANCER (IV)

PROSPETTIVE FUTURE

Una classificazione del k endocervicale correlato all'HPV sulla base del **pattern di invasione stromale** è stata recentemente proposta come **predittiva del rischio di metastasi linfonodali** ed è considerata uno strumento **utile per adattare l'approccio terapeutico** ed evitare un intervento chirurgico eccessivo in casi a basso rischio

Outcome data comparing the standard method of tumor evaluation (depth of invasion) versus the newly proposed pattern-based system.

	Patients	Patients with metastatic LN	# metastatic LNs	Stage I	Stages II–IV
Standard	352	49 (14%)	83 (1%)	320 (91%)	32 (9%)
Pattern A	73 (20.7%)	0	0	73 (100%)	0
Pattern B	90 (25.6%)	4 (4.4%)	5 (0.2%)	90 (100%)	0
Pattern C	189 (53.7%)	45 (23.8%)	76 (1.7%)	157 (83%)	32 (17%)

LNs: lymph nodes.

FIGO vs Pattern A/B/C

Comparison of FIGO stage vs. tumor pattern and recurrence.

	Stage								Total
	IA1	IA2	IB1	IB2	IB NOS	II	III	IV	
Recurrence/pattern A	0/14	0/8	0/46	0/1	0/4	0/0	0/0	0/0	0/73
Recurrence/pattern B	0/7	0/8	1/51 (2%)	0/4	0/20	0/0	0/0	0/0	1/90 (1.1%)
Recurrence/pattern C	0/4	0/10	14/107 (13%)	4/12 (33.3%)	6/24 (25%)	9/21 (43%)	3/6 (50%)	5/5 (100%)	41/189 (21.7%)

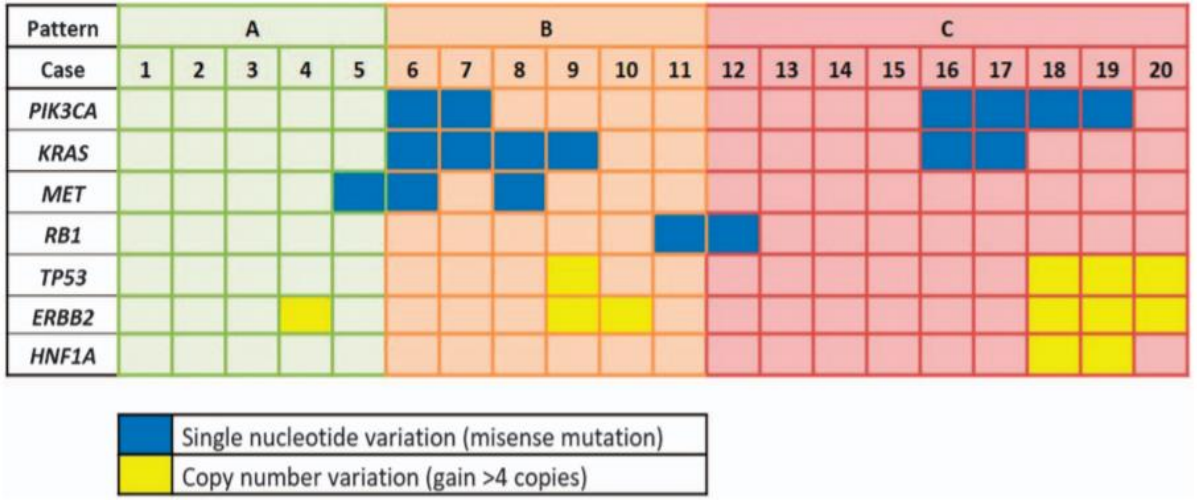
FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified.

I tumori con un pattern di **crescita non distruttivo (pattern A)** non presentano alcun rischio di metastasi linfonodali, rispetto a quelli con **invasione distruttiva focale (pattern B) o diffusa (pattern C)** (4% e 23%, rispettivamente)

Roma AA , Am J Surg Pathol 2015

ENDOCERVICAL CANCER (V)

Genomic abnormalities in invasive endocervical adenocarcinoma correlate with pattern of invasion: biologic and clinical implications



Management abbastanza standardizzato nel k squamoso esocervicale

Futuro panello diagnostico integrato anatomo-patologico/genomico per la gestione *tailored* dell'endocervice

Sulla base del **profilo genomico**, **le forme non distruttive di adenok** sembrano essere **biologicamente diverse da quelle distruttive.** Le lesioni con **pattern A** possono costituire **fasi iniziali** della progressione del tumore o vere e distinte **forme indolenti** di adenocarcinoma, mentre i **pattern B e C** rappresentano un più **aggressivo** sottoinsieme di neoplasia ghiandolare cervicale

In accordo con altre variabili prognostiche, la classificazione basata su tali pattern può servire come strumento di **triage per il test molecolare** al fine di valutare la prognosi e identificare i pazienti suscettibili di **trattamenti mirati**

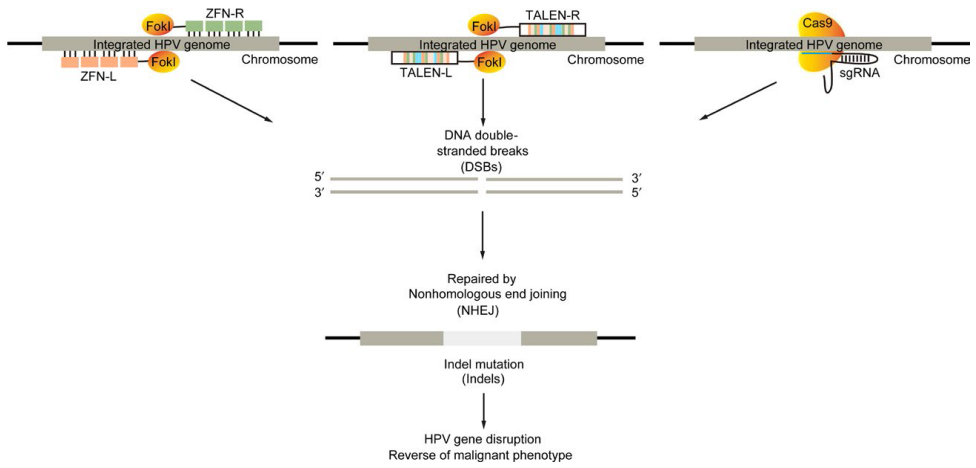
Hodgson et al, Modern Pathol 2017

CERVICAL CANCER (VI)

PROSPETTIVE FUTURE

Targeting HPV E6/E7 mRNAs with small interfering-RNA (siRNA) could effectively knock down their expression and induce apoptotic cell death in HPV-positive cell lines.

However, siRNAs only block HPV E6/E7 mRNAs temporarily, and they do not attack HPV DNA in the nuclei, which serves as a store of escape mutants that cause resistance to siRNA application. In recent years, artificially engineered genome editing techniques such as zinc finger nucleases (ZFNs), Tal-effector nucleases (TALENS), and the RNA-guided engineered nucleases (RGENs or CRISPR/Cas9) were used to cleave the specific DNA sequence of HPV. The double-stranded DNA breaks (DSBs) introduced by these custom-engineered endonucleases should trigger DNA repair pathways , resulting in the disruption of target viral oncogenes and the elimination of HPV infections

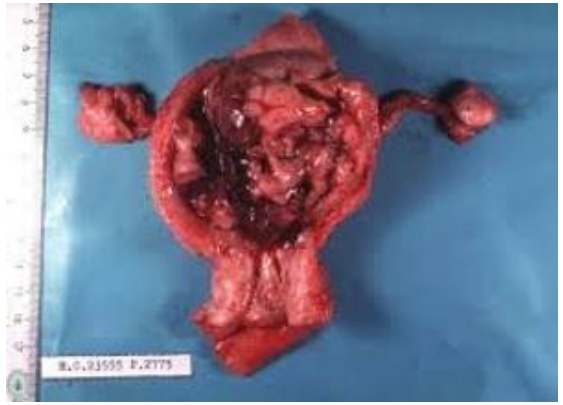


Hodgson et al, Modern Pathol 2017

Genome editing-based antiviral therapy may play valuable roles in HPV-related cervical carcinogenesis. If this therapy is appropriately combined with HPV testing, patients in precancerous stages, such as persistent HPV infections and their related CINs, would be able to take HPV testing first to determine the HPV subtype(s) and then select the corresponding type-specific genome editing tools to treat the appropriate HPV infection(s) and their related precancerous diseases. These patients would benefit from this new "screen-and-immediately-treat" strategy, instead of potential overtreatment including repeated screenings, colposcopy-directed biopsies, and cold knife conization. Consequently, additional costs, patient anxiety, and adverse effects that can result from repeated screenings, colposcopy-directed biopsies, and cold knife conization (e.g., vaginal bleeding and cervical insufficiency) could be avoided.

UTERINE SARCOMA (I)

Miomectomy is the **most common surgery** in gynecologic patients



Risk of sarcoma in women with **presumed fibroids** is **low**: 0,04- 0,12 %

Nonmetastatic leiomyosarcoma has a **63% 5-year survival rate** whereas **metastatic** leiomyosarcoma has a **14% 5-year survival rate**.

U.S. FOOD & DRUG ADMINISTRATION

2014 Food and Drug Administration safety communications

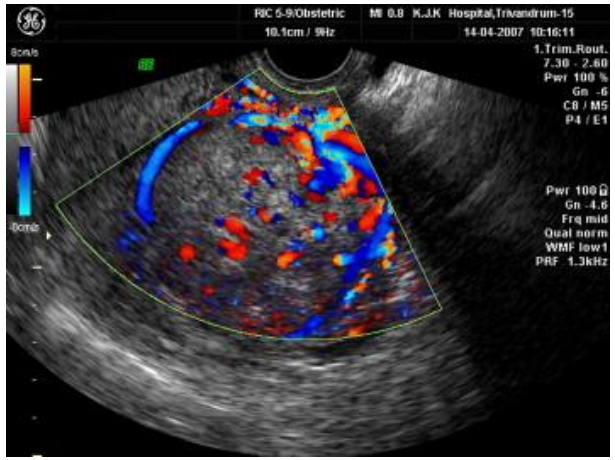
The FDA issued a **black-box warning** and stated that **morcellation was contraindicated in perimenopausal or postmenopausal women** and in "**candidates for en bloc tissue removal**" — ***"A category that, strictly speaking, encompasses all women"***

Seagle AJOG 2018
Siedhoff AJOG 2017

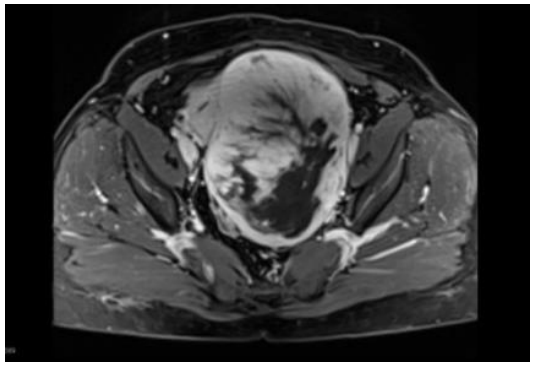
UTERINE SARCOMA (II)

IDENTIFICATION OF PREOPERATIVE CRITERIA

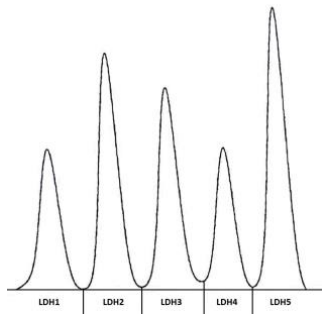
Ultrasound



MRI



Serum markers (LDH isozymes, Fibronectin, Tenascina, Laminin, OPN)



Novel genetic markers



Vercellini AJOG 2016
Siedhoff AJOG 2015

UTERINE SARCOMA (III)

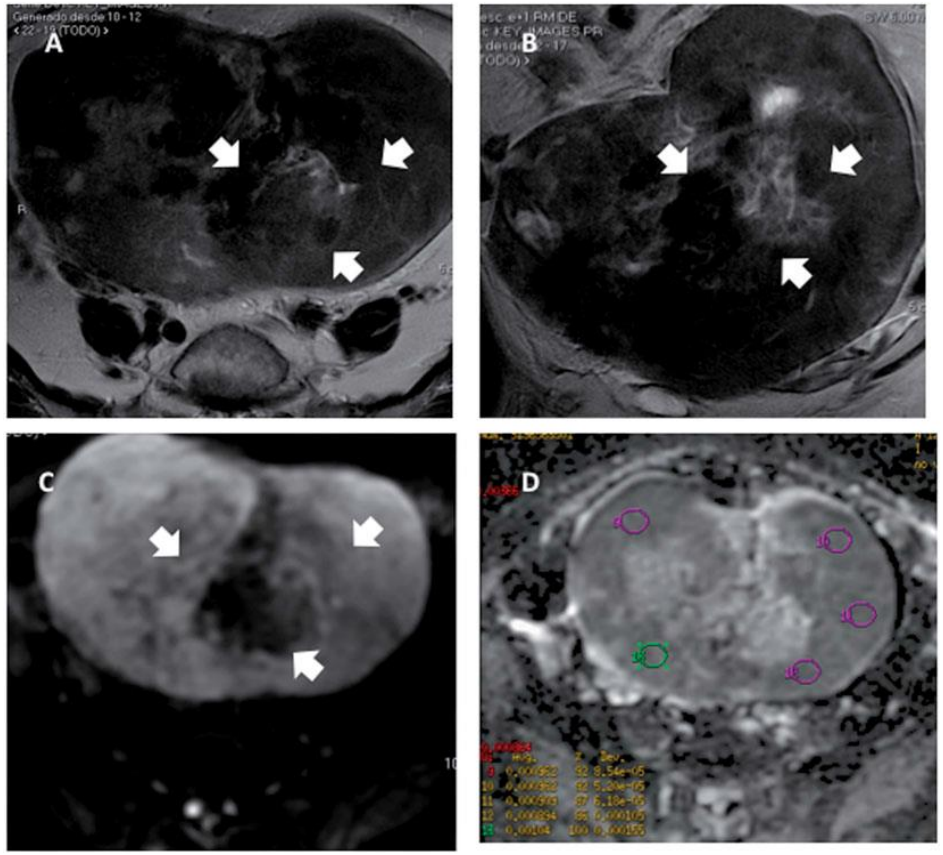
MRI

A computer-assisted method for distinguishing uterine sarcoma from leiomyomas based on perfusion weighted magnetic resonance imaging (PWI) showed an high diagnostic accuracy.
21 features extracted from the regions of interests (entire tumor, area of the lesion with the most marked contrast enhancement, psoas muscle, myometrium) were fed into the classifier an accuracy of 91.7%, sensitivity of 100%, and specificity of 90% were achieved.

Malek, Eur J Radiol. 2019

Diffusion-weighted magnetic resonance (DWMR) with the quantitative measurement of apparent diffusion coefficient (ADC) may be considered a useful preoperative test for the differentiation of atypical leiomyomas from sarcomas.
The ADC values equal or superior to $1x10^{-3}$ mm^2/s were always associated with a leiomyoma. The structural MR accuracy was 66.7%, reaching 100% when using DWMR with dichotomised ADC values.

Valdes-Devesa, J Obstet Gynaecol. 2019



UTERINE SARCOMA (IV)

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Full length article

A more accurate method to interpret lactate dehydrogenase (LDH) isoenzymes' results in patients with uterine masses

Annalisa Di Cello[a,*], Massimo Borelli[b], Maria Luisa Marra[a], Marco Franzon[c], Pietro D'Alessandro[d], Costantino Di Carlo[a], Roberta Venturella[a], Fulvio Zullo[d]

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[b] PhD School of PhD Programmes Life Sciences and technologies, University "Magna Graecia" of Catanzaro, Italy
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[d] Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples "Federico II", Naples, Italy

	U.M.G. ≤ 29	U.M.G. > 29	Total
Fibroids	2202	9	2211
Sarcomas	0	43	43
Total	2202	52	2254

U.M.G. index = LDH3 + 24/LDH1.
LDH: Lactate Dehydrogenase; U.M.G.= Uterine mass Magna Graecia.

SPECIFICITY: 99.6% (nine false positives over 2211 fibroids)
SENSITIVITY: 100%
LIKELIHOOD RATIO FOR A POSITIVE RESULT: 245.6
LIKELIHOOD RATIO FOR A NEGATIVE RESULT: 0.0

COMBINATION OF LDH, D-DIMER AND C-REACTIVE PROTEIN

Positive rates of LDH were 66.7%, 14.3% and 0% in groups S (sarcoma), PM (presumed malignant) and B (benign), respectively. Positive rates of D-dimer and C-reactive protein were 83.3% and 64.5%, 17.9% and 10.7% and 5% and 2.9% in groups S, PM and B, respectively.

When all parameters were positive, specificity and positive predictive value were 100% in differentiating leiomyosarcoma from presumed malignant group.

Combination of LDH, D-dimer and C-reactive protein could be useful for distinguishing leiomyosarcoma from especially degenerated or atypical leiomyoma.

Nishigaya, J Obstet Gynaecol Res. 2019

UTERINE SARCOMA (V)

A unique signature

A differential ***genetic*** and ***mi-RNA signatures*** were found for uterine sarcoma when compared to uterine fibroids, for primary LMS compared to the metastaticone, and for differential sarcoma hystotype.

Davidson et al., Gynecol Oncol 2013; Hum Pathol 2014
Ravid et al., Gynecol Oncol 2016

Genetic signature

ESS Overexpressed Genes

SLC7A10, EFNB3, CCND2, ECEL1, ITM2A, NPW, PLAG1 and GCGR.

LMS

TOPO2A, CDKN2A, FABP3, TAGLN, JPH2, GEM, NAV2 and RAB23.

Mutated Genes

Pten, P53, P16

mi-RNA signature

Deregulated mi-RNA

miR-200c, **let-7,**

a low expression of Let-7 (onco-suppressor) in uterine sarcoma compared to fibroids

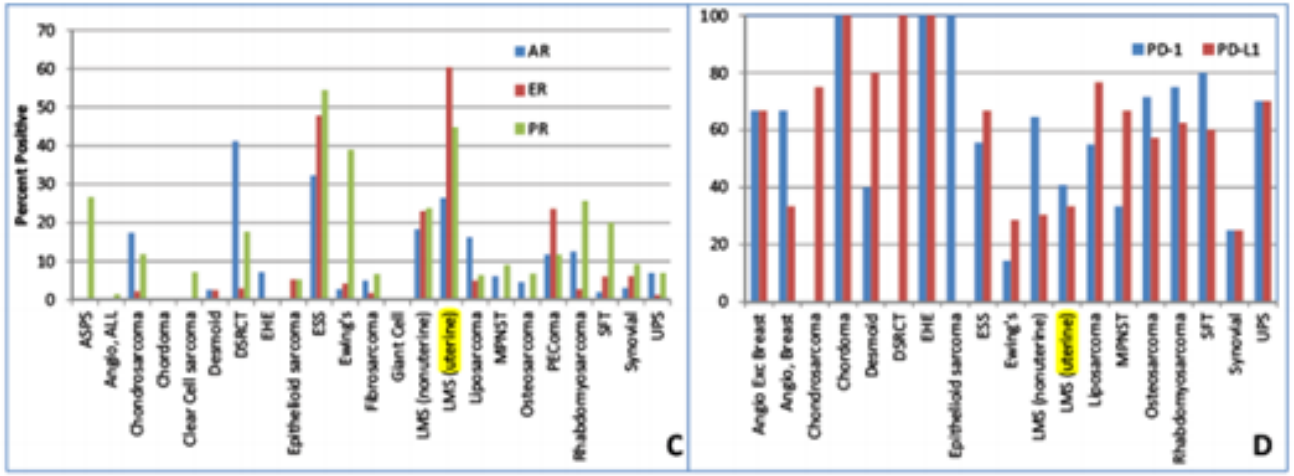
TOPO2A overexpression was found in 50% of sarcomas

NOVEL GENETIC MARKERS

Multi-platform profiling of over 2000 sarcomas: Identification of biomarkers and novel therapeutic targets

Sujana Movva[1,*], Wenhsiang Wen[2,*], Wangjuh Chen[2], Sherri Z. Millis[2], Zoran Gatalica[2], Sandeep Reddy[2], Margaret von Mehren[1], Brian A. Van Tine[3]

Movva et al., Oncotarget 2015



PRECISION MEDICINE AND FDA APPROVALS (I)

Anti-angiogenesis agents

Bevacizumab is the **only anti-angiogenic that is FDA approved** to treat gynecologic cancers, **in combination with chemotherapy**

Bevacizumab has been used with success in patients with **primary and recurrent ovarian cancer**. Improved **progression free survival** has been documented both in the upfront and recurrent settings

An **overall survival benefit has only been seen when used with standard chemotherapy, followed by bevacizumab maintenance**

Genentech submitted a supplementary biologic license that was recently approved, allowing **bevacizumab to be used with carboplatin and paclitaxel chemotherapy followed by maintenance** in women with newly diagnosed **advanced ovarian cancer**

Other VEGF and tyrosine kinase inhibitors, such as cediranib and nintedanib, **are currently being studied** for use in **ovarian and endometrial cancer**, but are currently available only in the setting of clinical trials

Bevacizumab has also received **FDA approval** for use in combination **with paclitaxel and cisplatin or paclitaxel and topotecan** for the treatment of **persistent, recurrent, or metastatic cervical cancer**, in which an **overall survival** benefit has been shown

Ovarian Cancer

Ovarian and endometrial cancers

Cervical cancer

Barroilhet, Gyn Onc 2018

PRECISION MEDICINE AND FDA APPROVALS (II)

PARP inhibitors

Since 2014, three PARP inhibitors have been FDA approved for the treatment of ovarian cancer

Ovarian Cancer

FDA approved PARP inhibitors.

	Olaparib (Lynparza)	Rucaparib (Rubraca)	Niraparib (Zejula)
Dosing	300 mg PO BID	600 mg PO BID	300 mg PO QD
Indications	Treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. 2. Maintenance treatment in patients with platinum-sensitive ovarian cancer who are in a complete or partial response to platinum-based chemotherapy, regardless of *BRCA* status	Treatment of patients with confirmed deleterious somatic or germline BRCA mutations, treated with 2 or more prior lines of chemotherapy	Maintenance treatment in patients with platinum sensitive ovarian cancer who are in a complete or partial response to platinum-based chemotherapy, regardless of *BRCA* status

Barroilhet, Gyn Onc 2018

PRECISION MEDICINE AND FDA APPROVALS (III)

Programmed death-1 inhibitors

Earlier this year, the FDA expanded the approval of **pembrolizumab** to include **tumors with microsatellite instability or mismatch repair deficiency** that have **not responded to prior therapy**

Le et al. expanded their work on colon cancer to include **other tumors with mismatch repair deficiencies**. Although survival data from this publication is not yet mature, **objective responses** were seen in **46 of the 86 patients (53%). Endometrial cancer patients** made up approximately **20%** of patients included in this study and were found to have the highest percentage (17%) of tumors with mismatch repair deficiency. This publication led to the **FDA approval of pembrolizumab** to treat **cancers with microsatellite instability**. It is the **first drug to receive FDA approval based on the presence of a specific abnormality in the tumor** itself

Endometrial cancer patients made up a small subset of the **KEYNOTE-028 study**. In a paper that focused on the cohort of endometrial cancer treated with **pembrolizumab** in the KEYNOTE-028 STUDY (n = 24), pembrolizumab showed activity in **previously treated patients with advanced PD-L1 positive endometrial cancers**. **Three** previously treated patients with advanced PD-L1 positive endometrial cancer had **responses** to pembrolizumab, with response duration as long as 65 weeks (data collection ongoing). **Three** additional patients had **stable disease**

Endometrial cancer

Endometrial cancer

Barroilhet, Gyn Onc 2018

PRECISION MEDICINE E PREVENZIONE

SCIENZA | VENERDÌ 19 GENNAIO 2018

Ci stiamo avvicinando a un test universale sul cancro

Una "biopsia liquida" con un esame del sangue permette di identificare 8 diversi tipi di tumore, con risultati molto promettenti

Caccia ai geni del cancro, all'Ieo di Milano super-test scova 115 mutazioni

L'Irccs di Veronesi realizza il sogno di Obama, un 'Oncochip' mapperà il rischio ereditario

Tumore al seno. In Usa via libera al primo test genetico fai da te per sapere se si è a rischio

Ma può rilevare solamente tre mutazioni dei geni Brca1 e Brca2 su più di mille esistenti

Ordina, sputa, scopri il risultato.

4 giugno 2018

Tumore al seno, test genetico consentirà a migliaia di donne di evitare la chemio

Inizia la nuova era dell'oncologia. In Italia interessate almeno 3mila donne l'anno



TAILORED PREVENTION

Identificazione precoce

Ricercare mutazioni *germline* **predisponenti** per identificare le **donne (e i familiari) con aumentato rischio di malattia**, da indirizzare a percorsi di sorveglianza e prevenzione personalizzati

Check up riproduttivo e di rischio oncologico

25-30 anni: eco-Tv + prelievo di sangue venoso per identificazione di **mutazioni genetiche predisponenti** e valutazione dell'**età ovarica**

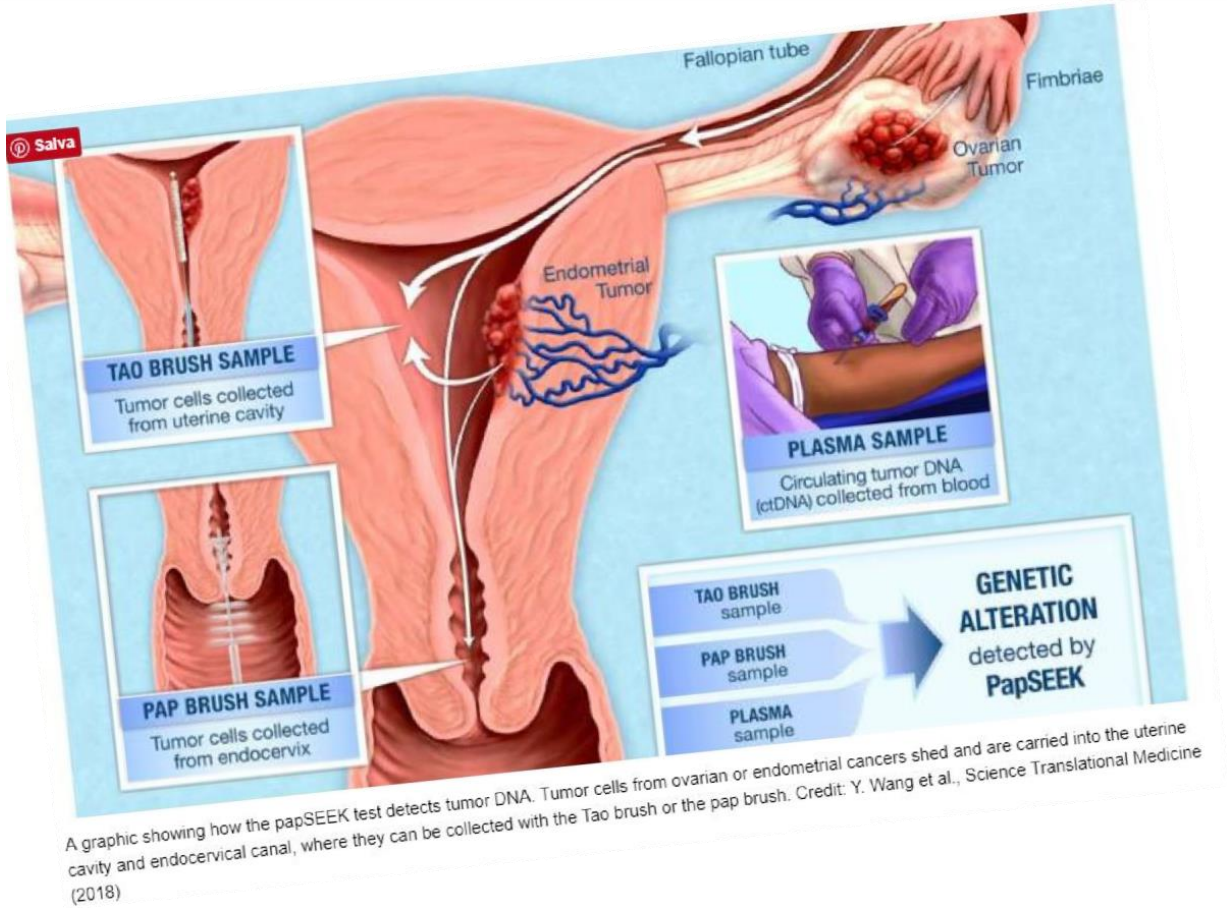
OvAge
Conosci, puoi



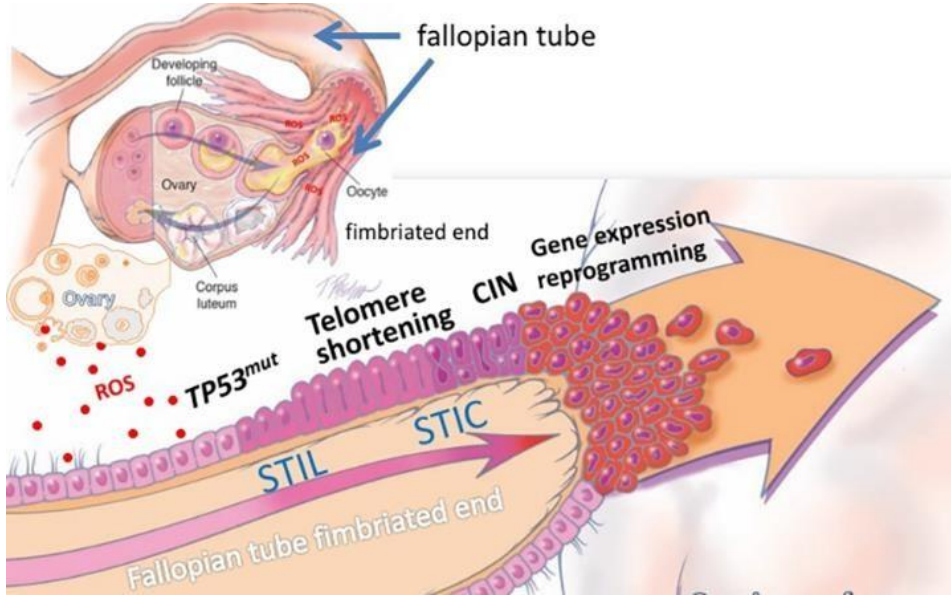
45 anni: prelievo isto-citologico endocervicale, endometriale ed endotubarico per identificazione del **rischio** e **diagnosi precoce** di **carcinomi endocervicale, endometriale, ovarico**



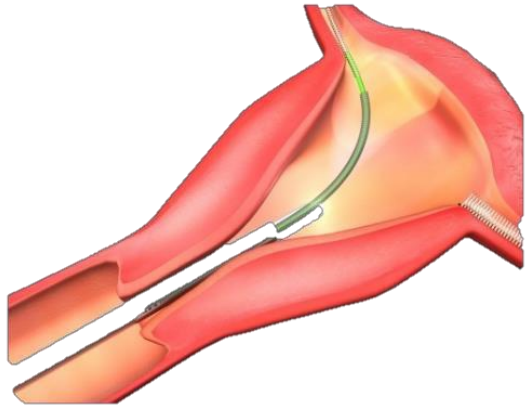
TAILORED PREVENTION E SCREENING UNIVERSALE



A graphic showing how the papSEEK test detects tumor DNA. Tumor cells from ovarian or endometrial cancers shed and are carried into the uterine cavity and endocervical canal, where they can be collected with the Tao brush or the pap brush. Credit: Y. Wang et al., Science Translational Medicine (2018)

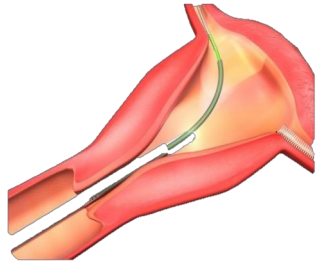


Prelievo isto-citologico endotubarico, endometriale ed endocervicale per via isteroscopica



TAILORED PREVENTION E SCREENING UNIVERSALE

CANCER	HISTOTYPE	GENE (SOMATIC MUTATION FREQUENCY)
OVARY	High-grade serous	TP53 (96%) CSMD3 (6%) FAT3 (6%) BRCA1 (3%) BRCA2 (3%) BARD1 RAD50 RAD51c-d PALB2 MRE11A NBN FANCM
	Endometrioid	TP53 (68%) ARID1A (30%) CTNNB1 (26%) PTEN (17%) PIK3CA (15%) KRAS (10%) PPP2R1A (11%) CDKN2A (12%) BRAF (8%)





CANCER	HISTOTYPE	GENE (SOMATIC MUTATION FREQUENCY)
OVARY	Clear cell	ARID1A (57%) PIK3CA (40%) PPP2R1A (7%) KRAS (4.7%) MAP2K6 (also endometrioid) KIAA1324 (also endometrioid) CDH1 (also endometrioid) ENTPD5 (also endometrioid) LAMB1 (also endometrioid) DRAM1 (also endometrioid) CCNB2 (also endometrioid) CORO2A (also endometrioid) CSNK1G1 (also endometrioid) FRMD8 (also endometrioid) LIN54 (also endometrioid) LINC00664 (also endometrioid) PDK1 (also endometrioid) PEX6 (also endometrioid) EPCAM MLH1 MSH2-6 PSM2

CANCER	HISTOTYPE	GENE (SOMATIC MUTATION FREQUENCY)
OVARY	Low-grade serous	BRAF (38%) KRAS (19%)
	Mucinous	TP53 (56%) KRAS (40%) PPP2R1A (33%) CDKN2A (16%) PTEN (11%) HER2 PDGFRA (6.6%) KIT (2.2%) HRAS (2.2%) MET (2.2%) IMP3 RNF43, ELF3, ERBB3, KLF5 (<7%)
	Tumori rabdoidi maligni	SMARCB1
	Tumori dei cordoni sessuali	STK11

CANCER	HISTOTYPE	GENE (SOMATIC MUTATION FREQUENCY)
CERVIX	Endocervical adenocarcinoma	HPV histotype: 18,31,45 KRAS ARID1A PTEN PIK3CA MET RB1 TP53 ERBB2 HNF1A

CANCER	HISTO TYPE	GENE (SOMATIC MUTATION FREQUENCY)
ENDOMETRIUM	Endometrioid	PTEN (64%) PIK3CA (59%) ARID1A (55%) CTNNB1 (32%) MLL2 (32%) FBXW7 (27%) RNF43 (27%) APC (23%) FGFR2 (18%) KRAS (9%) PIK3R1 (9%) EGFR (14%) AKT1 (5%) NRAS (5%) TP53 (5%) POLE (7%) EPCAM MLH1 MSH2-6 PSM2 PAX2 BCL-2
	Serous	TP53 (5%) PIK3CA (24%) FBXW7 (20%) PPP2R1A (18%)
	Clear cell	TP53 (45%) PPP2R1A (33%) PIK3CA (29%) PTEN (13%) PIK3R1 (9%) KRAS (5%)

TAILORED PREVENTION

Sorveglianza personalizzata in base al rischio individuale

Creare **algoritmi di sorveglianza personalizzati**, con tempistiche e integrazioni di valutazioni prognostiche individualizzate sulla specifica paziente con quel particolare fattore di rischio

Sorveglianza annuale
su utero e ovaie

Chirurgie profilattiche
desiderio riproduttivo completato

Programmazione riproduttiva
rispettosa di questa predisposizione



Approfondimento delle indagini
tailored

TAILORED PREVENTION E CANCRO ENDOMETRIALE

Sorveglianza e prevenzione personalizzata in base al rischio individuale

Nuovo pannello diagnostico per le iperplasie endometriali che non regrediscono dopo terapia medica

P53
MMR
Beta-catenina
L1CAM
TILs



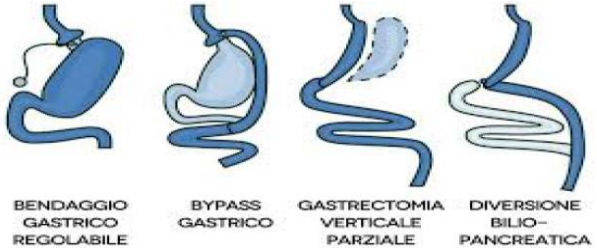
Nelle pz a rischio, pannello diagnostico alla prima comparsa di iperplasia endometriale

PAX2 [1]
Bcl2 [2]
Beta-Catenina [3]
ARID1A [4]
ER [5]
PR [5]





Lo **IUD medicato al levonorgestrel** è una strategia di **prevenzione** delle morti per cancro dell'endometrio potenzialemte **efficace** in donne **obese** con un **ottimo rapporto costi-benefici.**
Rischio di cancro endometriale **ridotto del 78%.**



Rischio di cancro endometriale ridotto fino all'81% in donne **obese** che ottengono e mantengono una **riduzione di peso mediante chirurgia bariatrica**



Anche l'uso di **metformina da sola o in combinazione** con la terapia standard **potrebbe ridurre il rischio** di carcinoma endometriale

[1] *Raffone, Acta Obstet Gynecol Scand. 2018*
[2] *Travaglino, Acta Obstet Gynecol Scand. 2018*
[3] *Travaglino, Submitted to Int J Gynecol Pathol*
[4] *Raffone, Submitted*
[5] *Raffone, Acta Obstet Gynecol Scand. 2018*

Dottino, Obstet Gynecol. 2016
Mackintosh, Gynecol Oncol. 2018
Mie Jareid, Gynecol Oncol. 2018

TAILORED PREVENTION E CANCRO CERVICALE

Sorveglianza personalizzata in base al rischio individuale

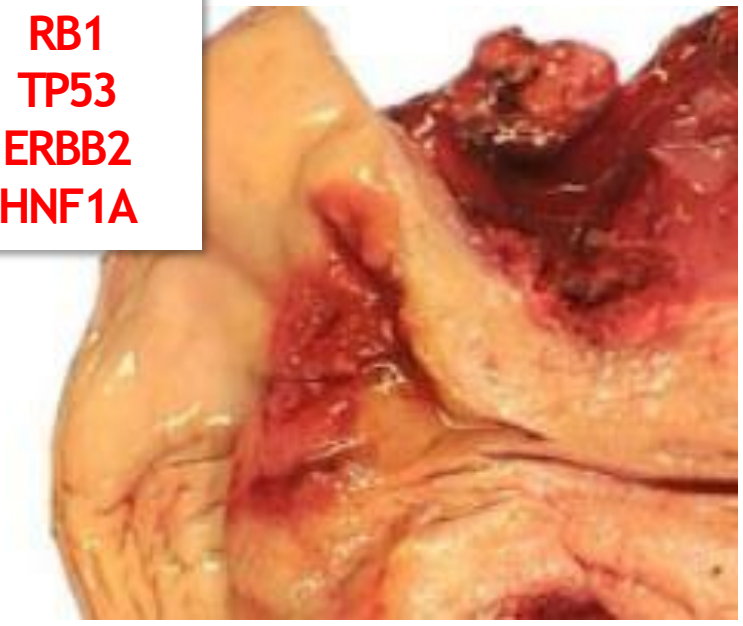
Nuovo pannello diagnostico per le persistenze di HPV ad alto rischio

ZNF516
FKBP6
INTS1
E6
E7
VEGF



Nuovo pannello diagnostico per le pz con AGC-NOS o AGC

PIK3CA
KRAS
MET
RB1
TP53
ERBB2
HNF1A

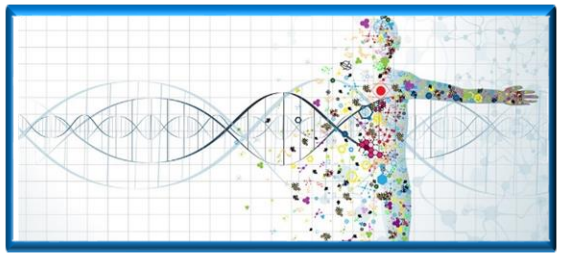


TAKE HOME MESSAGES

NUOVO APPROCCIO ALLA PAZIENTE

INTEGRATO

TAILORED

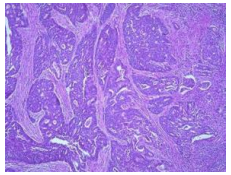


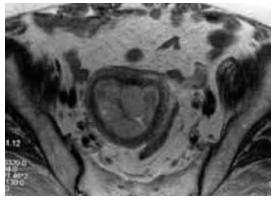


Anatomia Patologica

Ginecologia

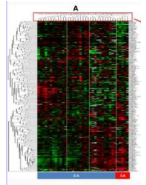
Oncologia





PAZIENTE

Genetica



Radioterapia

Medicina di laboratorio

Diagnostica per immagini



"the **right therapy**, at the **right time**, in the **right patient**..."

Capacità chirurgica



Cultura multidisciplinare

TAKE HOME MESSAGES

✓E’ necessaria una critica revisione del processo decisionale nel trattamento delle pazienti oncologiche

✓La Precision Medicine può divenire il fattore determinante per la riduzione della mortalità, ma ancor più nella prevenzione primaria e nei protocolli di sorveglianza personalizzati

✓I dati genomici ottenuti mediante surrogati immunoistochimici (a basti costi e ampiamente utilizzabili nella comune pratica clinica) rappresenteranno la pietra angolare del miglioramento terapeutico

XIX Congresso Nazionale A.G.E.O.

PREDITTIVITÀ E DIAGNOSI PRECOCE IN OSTETRICIA E GINECOLOGIA



Lettura magistrale

La battaglia contro il cancro e la medicina predittiva

Fulvio Zullo



GRAZIE