Il ruolo della genetica in oncologia ginecologica: ieri, oggi e domani.

Pierandrea De Iaco

pierandrea.deiaco@unibo.it

GYNECOLOGIC ONCOLOGY
SANT'ORSOLA-MALPIGHI HOSPITAL
BOLOGNA - ITALY

npj | Precision Oncology

www.nature.com/npjprecisiononcology

COMMENT OPEN

Precision medicine: the foundation of future cancer therapeutics

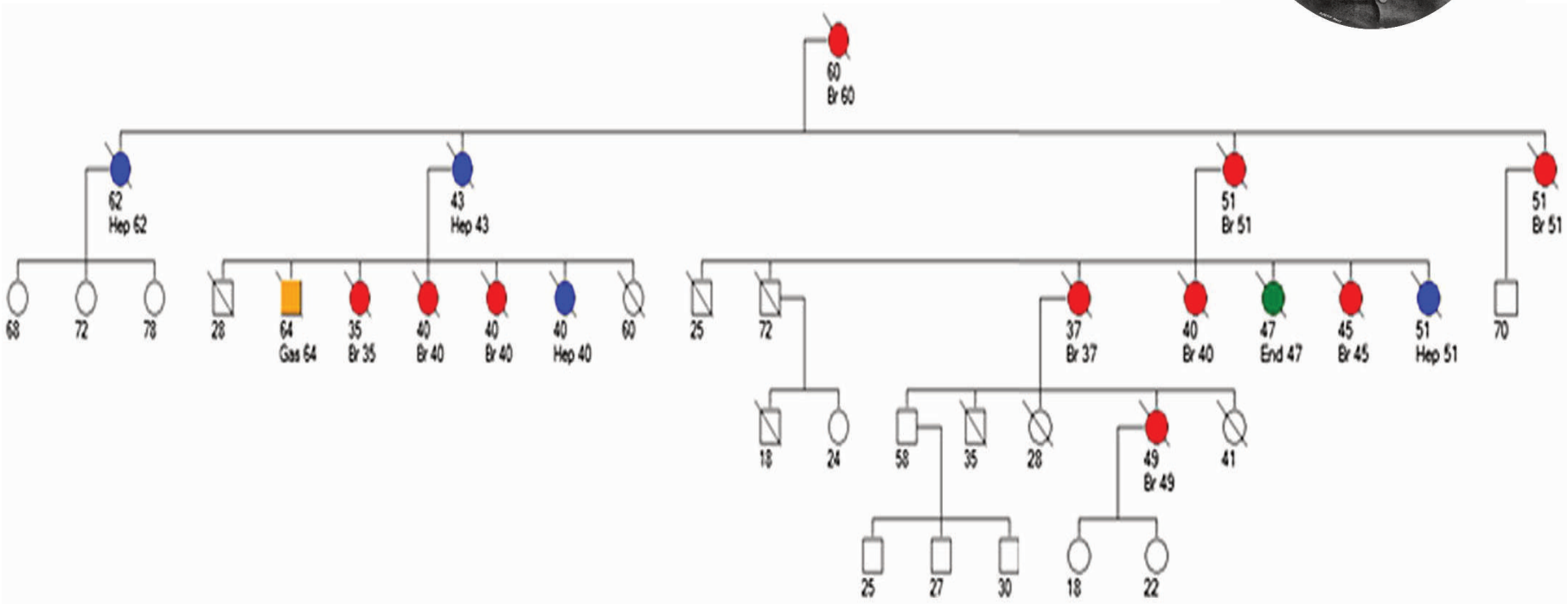
Seung Ho Shin[1], Ann M. Bode[1] and Zigang Dong[1]

npj Precision Oncology (2017)1:12; doi:10.1038/s41698-017-0016-z

GENETICA E ONCOLOGIA

- **Analisi genetica**
  - Analisi cellule tumorali (somatico)
  - Analisi cellule germinali
- **Studio familiarità tumorale**
  - Screening per familiari
  - Chirurgia di riduzione del rischio
- **Prospettive terapeutiche chirurgiche**
  - Chirurgia gene-modulata
- **Prospettive terapeutiche mediche**
  - Farmaci diretti su target genici
- **Nuovi geni nella oncogenesi**

A hereditary breast cancer family described by Paul Broca in 1866

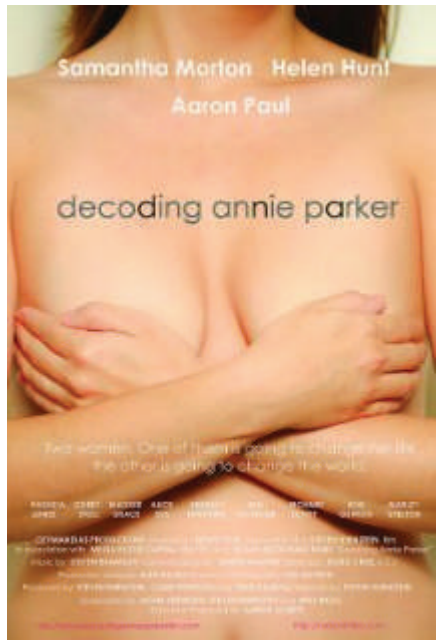


Red circles denote women diagnosed with breast cancer, blue is liver cancer, orange gastric cancer, and green endometrial cancer. Pedigree drawn with CaGene6

Euhus DM and Robinson L. *Surg Clin North Am*, 2013

Factors that predict a breast/ovary risk

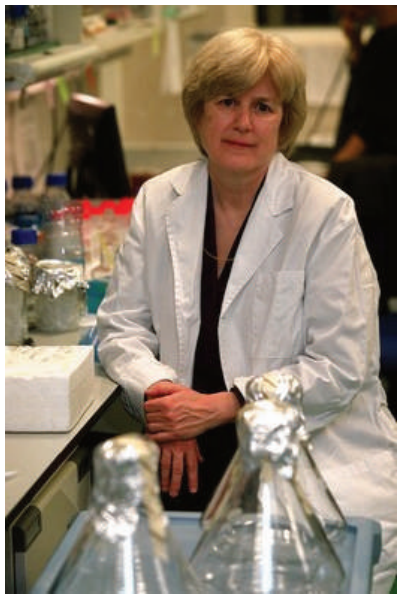
- **Ethnic group** (for example, Aashkenazi Jewish)
- **Young age** (<50 years) of the onset of breast cancer (mostly for triple negative disease)
- **Invasive ovarian cancer** (any age)
- **Family history** of breast or ovarian cancer



Narod SA. Nat Rev Clin Oncol 2010

Hereditary breast and ovarian cancer BRCA 1 / 2

- Identificati nel 1994-95
- Geni oncosoppressori
- Cromosoma **17 e 13**
- Trasmissione **AD** (materna o paterna)



Mary-Claire King,

Mike Stratton

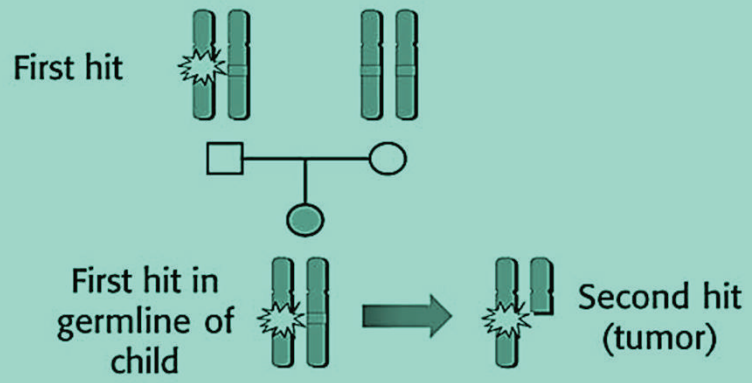
Richard Wooster

Modello del "double-hit" di Knudson

Negli individui che ereditano una mutazione in un gene onco-soppressore, il 1° colpo viene ereditato come mutazione germinale e il 2° colpo si verifica in una cellula somatica

Alfred Knudson

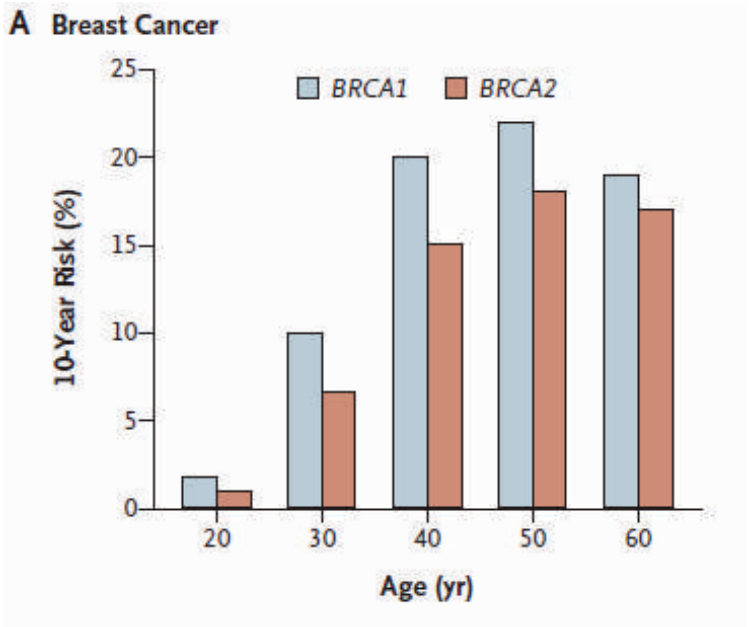
The Two-Hit Hypothesis

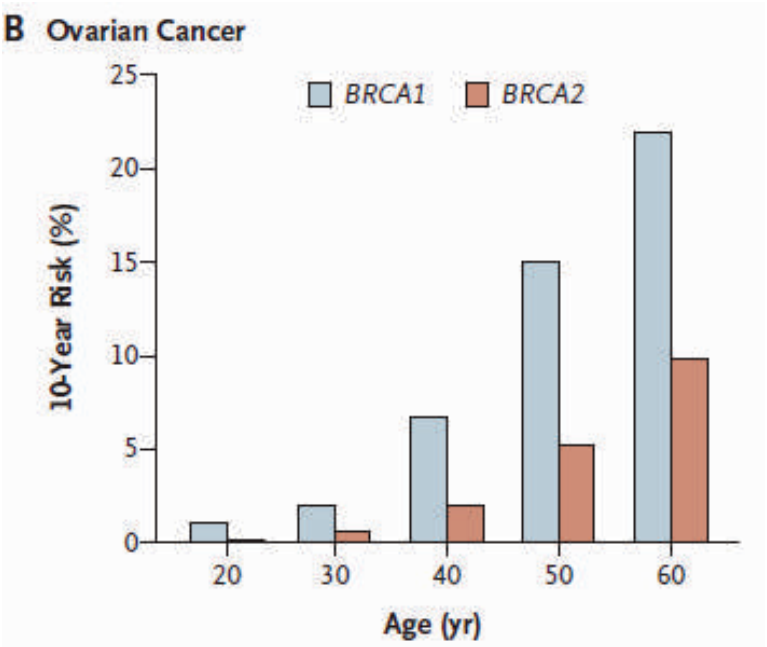


Jorde LB, Carey JC, White RL. *Medical Genetics*. 2nd ed. St Louis: Mosby; 2000.
Knudson AG. *Proc Natl Acad Sci U S A*. 1971;68:820-823.

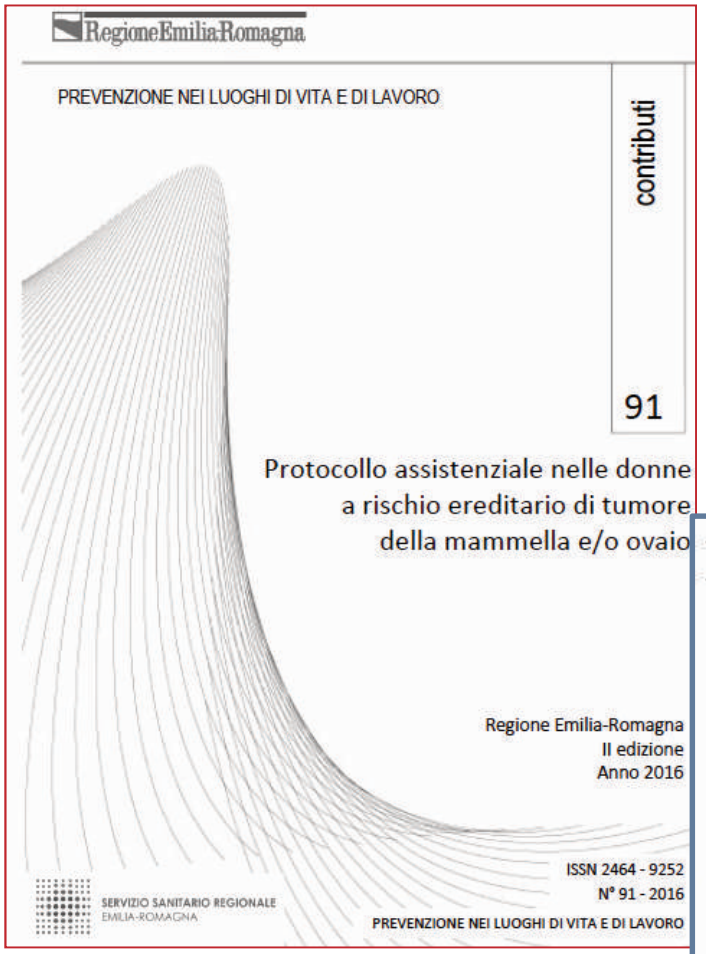
Rischio associato a mutazioni di BRCA1/2

	BRCA1	BRCA2
Carcinoma mammario	57 %	49 %
Carcinoma ovarico	40 %	18 %





Chen and Parmigiani, JCO 2007, Robson M, Offit K, N Engl J Med 2007



http://www.saluter.it/documentazione/rapporti/contributi

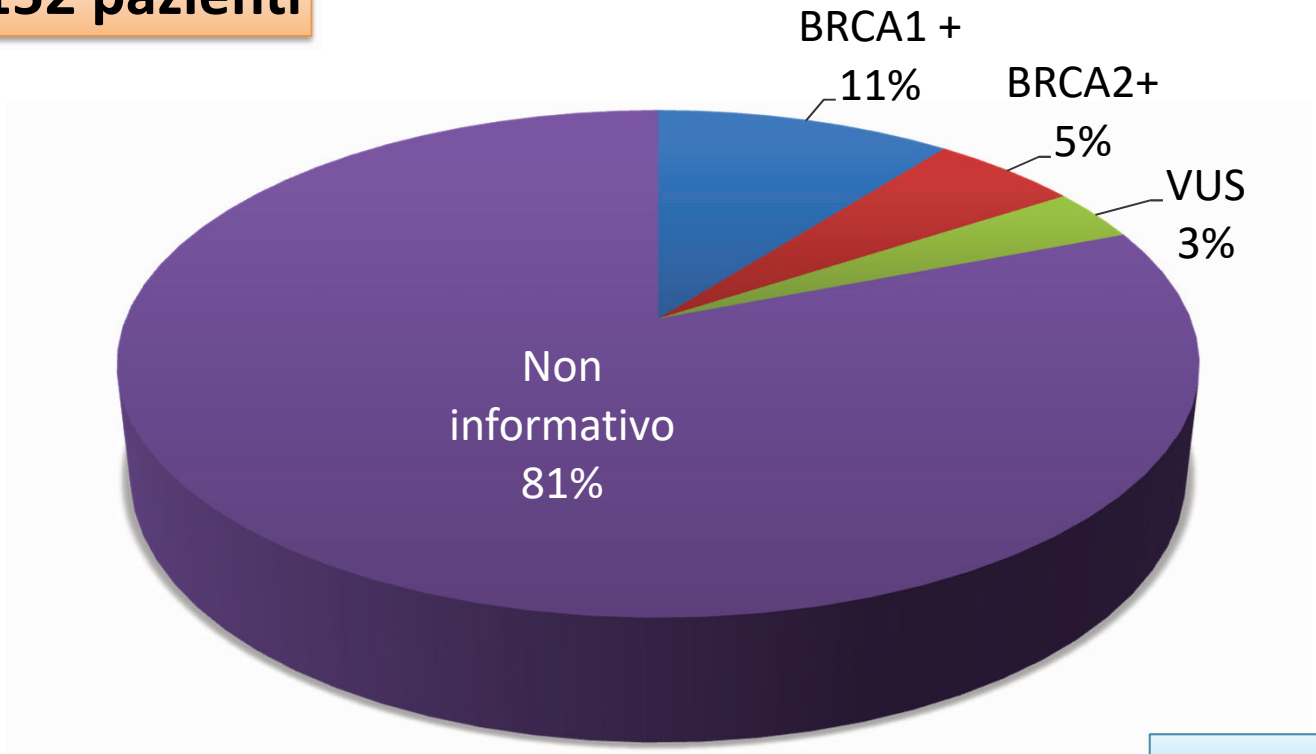
Criteri di accesso al test genetico

Nell'ambito del percorso di consulenza genetica è appropriata l'esecuzione del test genetico di ricerca di mutazioni di BRCA1 e BRCA2 quando sia soddisfatto ***almeno uno*** dei seguenti criteri:

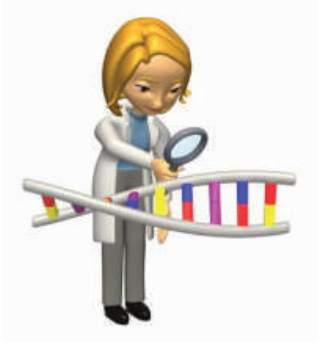
1) Breast Ovarian Cancer (BOC): Pazienti affette da tumore sia mammario che ovarico.
2) Carcinoma ovarico (CO), delle tube di Falloppio e primitivo peritoneale non mucinoso e non borderline a qualsiasi età, con o senza familiarità, o più casi di CO.
3) Hereditary Breast and Ovarian Cancer (HBOC): Famiglie con ≥ 1 caso carcinoma ovarico associato a ≥ 2 carcinomi mammari di cui uno ≤ 40 anni o bilaterale e parentela di I grado tra i 3 individui.
4) Carcinoma mammario e ovarico sospetto ereditario (SHBOC): 3 o più pazienti affetti da carcinoma mammario/ovarico con parentela di I grado senza giovane età o bilateralità, oppure con giovane età o bilateralità ma senza parentela di I grado.
5) Hereditary Breast Cancer (HBC): 3 o più pazienti affette da carcinoma mammario, di cui uno entro i 40 anni o bilaterale e parentela di I grado tra i 3 individui.
6) Carcinoma mammario e ovarico fortemente sospetto per familiarità (SFBOC+): 1 paziente affetta da carcinoma mammario e 1 da carcinoma ovarico con familiarità di I grado e ≤40 anni o bilateralità.
7) Early Onset Breast Cancer (EOBC): Pazienti affette in età ≤35 anni senza familiarità.
8) Male Breast Cancer (MBC): Paziente affetto da carcinoma mammario maschile.
9) Familiare per carcinoma mammario ed ovarico (FBOC): 3 pazienti affetti da carcinoma mammario ed ovarico senza essere HBOC o SHBOC.
10) Fortemente sospette per familiarità per carcinoma mammario (SFBC+):2 casi parenti di I grado, di cui 1 con età ≤ 40 anni o bilaterale.
11) Carcinoma mammario duttale infiltrante G3 "triplo negativo" (RE=negativo; RPg=negativo, c-Erb=negativo), in età ≤60 anni.

Risultati test BRCA nelle pazienti con carcinoma ovarico (2017 + 1° semestre 2018)

152 pazienti



AGO-BO



Blood

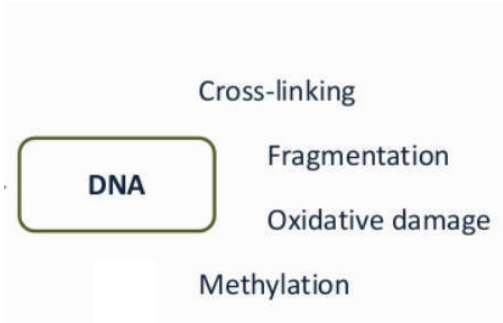
DNA Extraction

Test BRCA germinale
(solo mutazioni costituzionali)

Cancer Patient

FFPE Sample

DNA Extraction



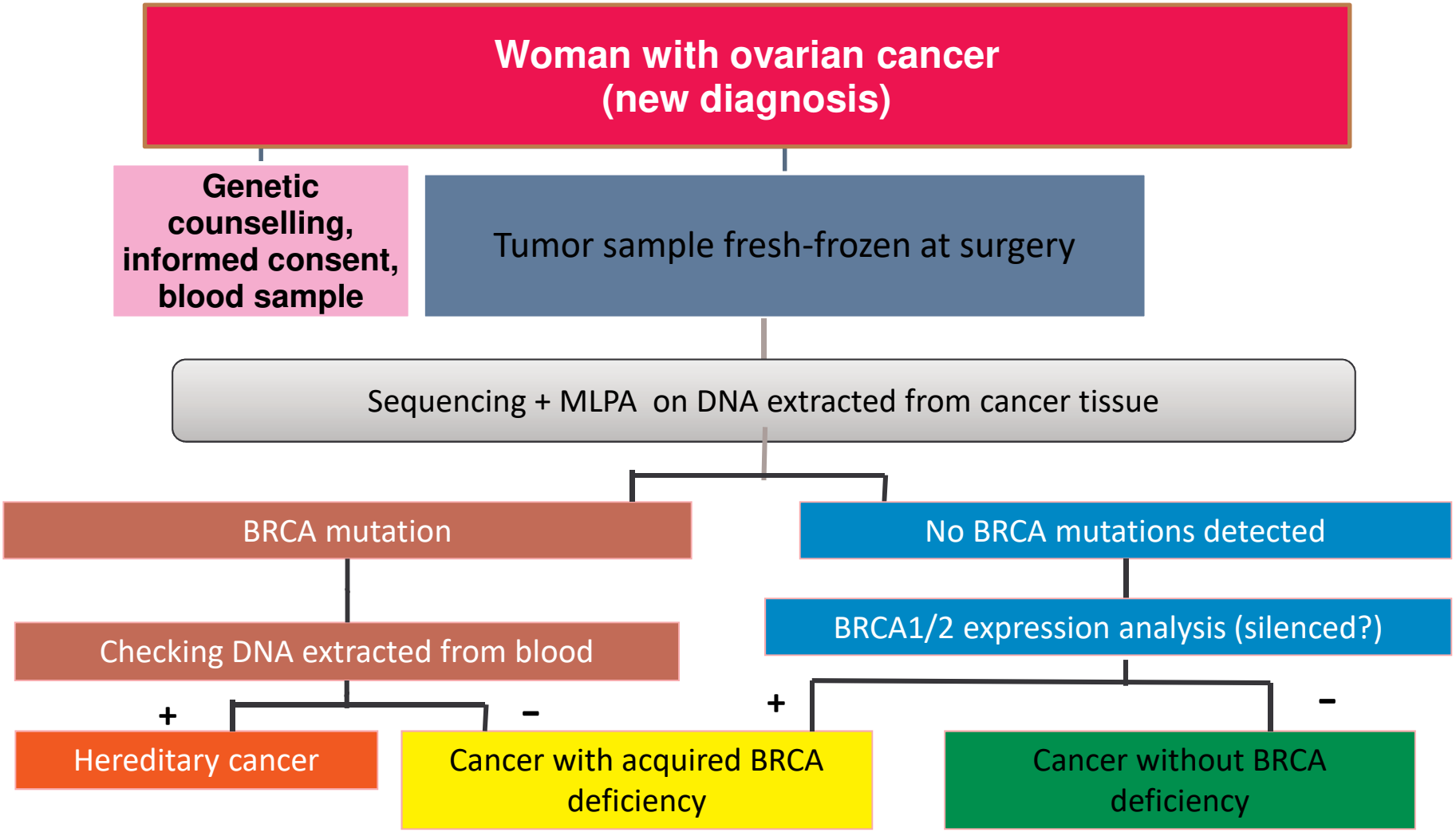
Fresh-frozen tissue

DNA Extraction

Test BRCA somatico
(mutazioni costituzionali e acquisite)

The GECO project

Caratterizzazione GEnetica del Carcinoma Ovarico



Pazienti con nuova diagnosi

SSD Oncologia Ginecologica

- Consulenza pre-test
- Consenso informato
- Prelievo di sangue
- Richieste
  - Anatomia Patologica
  - Genetica Medica

UO Anatomia Patologica

- Preparazione sezioni per Genetica Medica (selezione tessuto tumorale)

UO Genetica Medica

- Test **BRCA somatico**
- Verifica varianti su sangue

Nessuna variante

Referto a Ginecologo richiedente

Comunicazione paziente

Variante

Consulenza genetica

Pazienti con diagnosi pregressa

Oncologo o Ginecologo

- Consulenza pre-test
- Consenso informato
- Prelievo di sangue
- Acquisizione sezioni presso Anatomia Patologica di riferimento (percorsi da definire localmente)

UO Genetica Medica

- Test **BRCA somatico** →Verifica varianti su sangue
- oppure, in assenza di tessuto tumorale:
  - Test **BRCA costituzionale**

+

- **Eventuale test somatico in paziente con pregresso test costituzionale negativo, candidata a terapia**

Nessuna variante

Referto a medico richiedente

Comunicazione paziente

Variante

Consulenza genetica

GENETICA E ONCOLOGIA

- **Analisi genetica**
  - Analisi cellule tumorali (somatico)
  - Analisi cellule germinali
- **Studio familiarità tumorale**
  - Screening per familiari
  - Chirurgia di riduzione del rischio
- **Prospettive terapeutiche chirurgiche**
  - Chirurgia gene-modulata
- **Prospettive terapeutiche mediche**
  - Farmaci diretti su target genici
- **Nuovi geni nella oncogenesi**

Gestione del rischio ereditario in donne BRCA 1 e 2

Rischio di *neoplasia ovarica*

BRCA 1: 35-60%

BRCA 2: 10-27%

family history OC : 5%

Premessa

- ***"Neoplasia ovarica" :*** tumori che possono originare **dall'ovaio, tuba e peritoneo**

- fenotipi comuni associati alle donne BRCA
  - sono **sieroso-papillifero e endometrioide** ad alto grado (**tipo II**)
  - non si osservano mucinosi e borderline

Boyd J et al JAMA 2000

Sorveglianza clinico strumentale in donne BRCA 1 o 2
LINEE GUIDA

ACOG 2009

Opzioni	Intervallo	Età di inizio
Ecografia TV	periodico	30-35 anni
CA125	periodico	30-35 anni

NB: inizio 5-10 anni prima dell'insorgenza della malattia nel familiare

NCCN 2014

Opzioni	Intervallo	Età di inizio
Ecografia TV	6 mesi	30 anni
CA125	6 mesi	30 anni

NB: inizio 5-10 anni prima dell'insorgenza della malattia nel familiare

Table 2. Hazard Ratios (HRs) of Death Associated With Various Treatment Factors

	Univariate		Multivariate[a]	
Treatment Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Breast Cancer-Specific Death				
Chemotherapy	0.92 (0.62-1.34)	.65	0.70 (0.43-1.15)	.16
Oophorectomy[b]	0.47 (0.29-0.76)	.002	0.46 (0.27-0.79)	.005
Ipsilateral mastectomy (vs lumpectomy)[b]	1.03 (0.70-1.50)	.90	1.19 (0.75-1.89)	.45
Contralateral mastectomy[b]	0.60 (0.37-0.96)	.03	0.59 (0.34-1.04)	.07
All-Cause Mortality				
Chemotherapy	0.91 (0.66-1.27)	.58	0.76 (0.50-1.15)	.19
Oophorectomy[b]	0.39 (0.25-0.59)	<.001	0.35 (0.22-0.56)	<.001
Ipsilateral mastectomy (vs lumpectomy)[b]	0.95 (0.69-1.32)	.77	1.23 (0.83-1.86)	.30
Contralateral mastectomy[b]	0.54 (0.36-0.82)	.004	0.56 (0.34-0.91)	.02

[a] Adjusted for age at diagnosis, year of diagnosis, *BRCA* gene (*BRCA1* or *BRCA2*), tumor size (in centimeters), nodal status (positive/negative), estrogen receptor status (positive, negative, missing), receipt of chemotherapy, tamoxifen use, oophorectomy, contralateral mastectomy (yes/no), and ipsilateral mastectomy (vs lumpectomy).

[b] Time-dependent variable.

CONCLUSIONS AND RELEVANCE

Oophorectomy is associated with a decrease in mortality in women with breast cancer and a *BRCA1 mutation.*

Women with estrogen receptor–negative* breast cancer and a *BRCA1 mutation should undergo oophorectomy shortly after diagnosis.

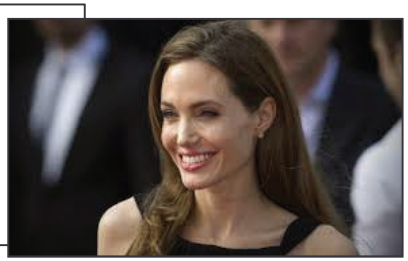
RRSO and risk of gynecologic and breast cancer

Study	Design	No. of BRCA1/2 carriers with salpingo-oophorectomy	No. of BRCA1/2 carriers without salpingo-oophorectomy	Gynaecologic cancers HR (95% CI)	Breast cancer HR (95% CI)
Kauff et al. [65]	Prospective	98	72	0.15 (0.02–1.31)	0.32 (0.08–1.20)
Rebb					
Rutte					
Eisen					
Dom					
Finch					
Chang-Claude et al. [69]	Retrospective	55	1601	NA	0.56 (0.29–1.09)
Kauff et al. [70]	Prospective	509	283	0.12 (0.03–0.41)	0.53 (0.29–0.96)
Rebbeck et al. [71]	Meta-analysis of 10 studies			0.21 (0.12–0.39)	0.49 (0.37–0.65)

RRSO reduces the risk of developing ovarian/ tubal cancer by 80-95%

Gadducci et al. Gynecological Endocrinology, 2010,26:568-577

BRCA 1 e 2 e ANNESSIECTOMIA PROFILATTICA



La **salpingo-ovariectomia bilaterale**

- Riduce del 95% il rischio di carcinoma ovarico
- Se effettuata **prima dei 40 anni riduce il rischio di carcinoma mammario del 64% in BRCA 1** e del **31% in BRCA2**

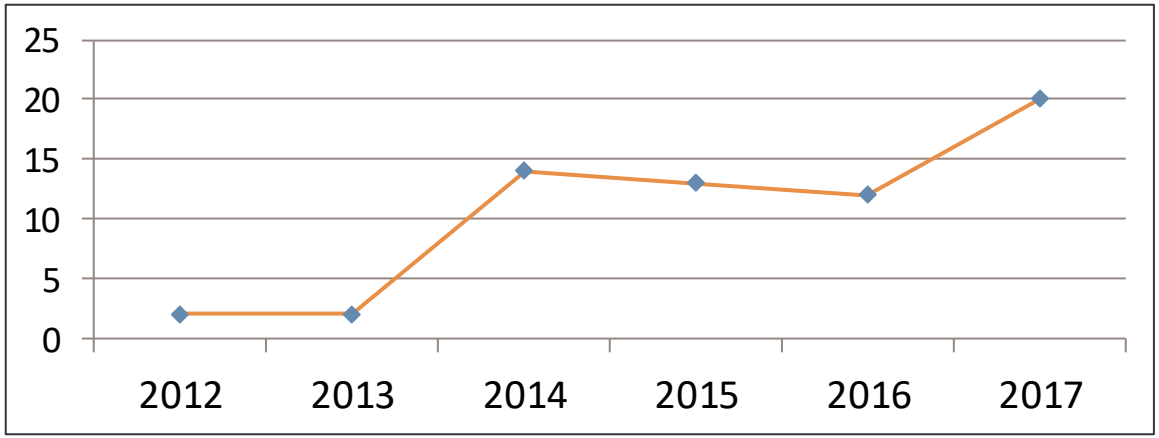
Eisen A et al. J Clin Oncol 2005
Rebbeck TR e al. J Natl cancer Inst 2009

BRCA 1 / 2 e CHIRURGIA PROFILATTICA

CRITERI PER CONSIDERARE LA CHIRURGIA SULL'APPARATO GENITALE

- Donne di **età maggiore dei 35-40 anni** che hanno completato il loro ciclo riproduttivo
- Le aspettative di vita della donna non devono essere ridotte da malattie gravi
- Sebbene la scelta definitiva sia strettamente personale, **l'opzione chirurgica deve essere discussa ad un meeting multidisciplinare**
- La donna deve essere protetta dallo sviluppo di un tumore, dalle complicanze e devono essere considerati gli aspetti sessuali e psicologici
- **Discussione sul tipo di intervento** (BSO o ITAB) **LAPAROSCOPICO**
- Deve essere offerto un **supporto psicologico**

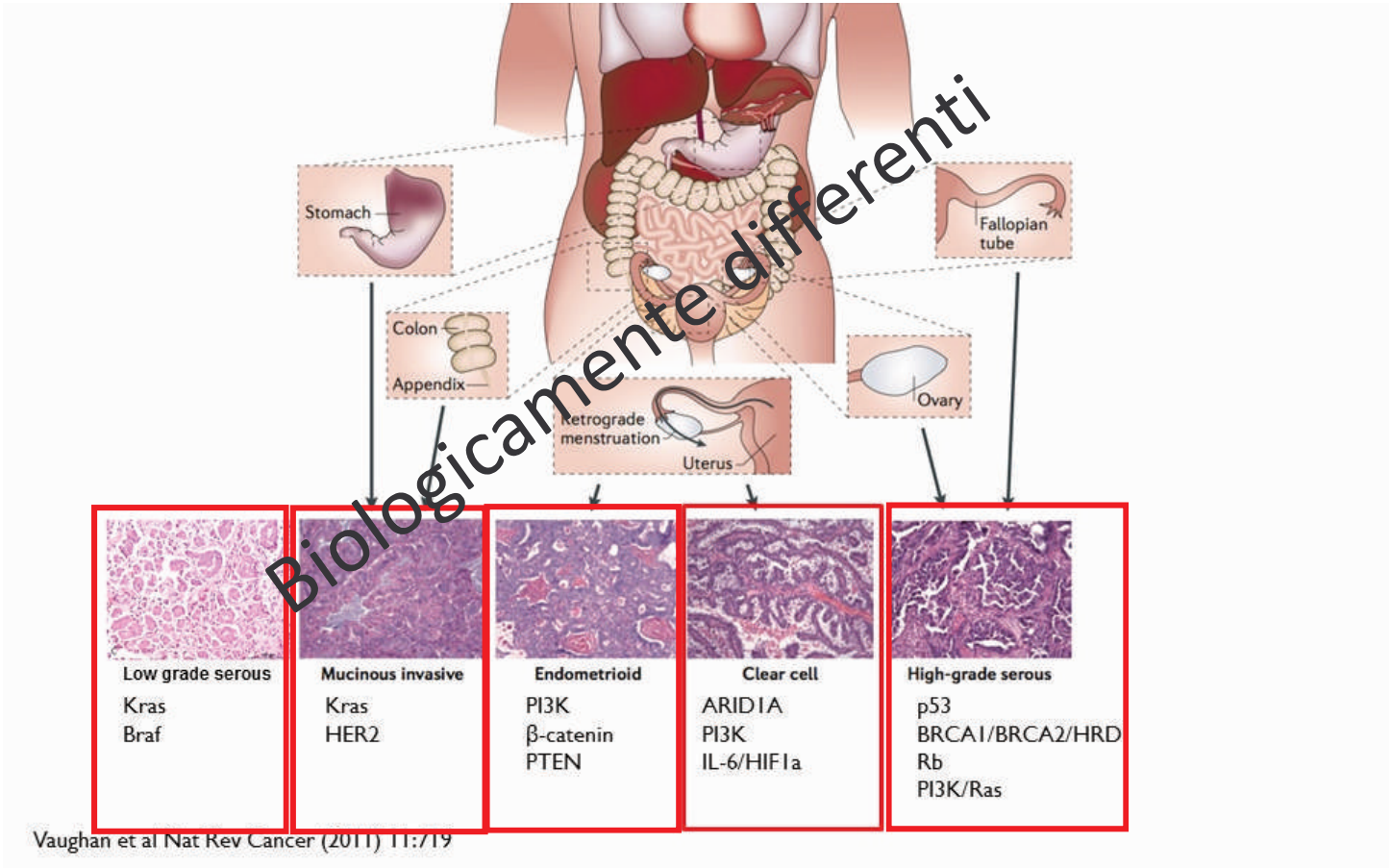
ANNESSIECTOMIA PROFILATTICA
in pazienti BRCA positive
Anni 2012-2015



Età	**media 50 anni (range 36-75)**	
	≤ 40	16%
	41-45	23%
	46-50	23%
	>50	38%

GENETICA E ONCOLOGIA

- **Analisi genetica**
  - Analisi cellule tumorali (somatico)
  - Analisi cellule germinali
- **Studio familiarità tumorale**
  - Screening per familiari
  - Chirurgia di riduzione del rischio
- **Prospettive terapeutiche chirurgiche**
  - Chirurgia gene-modulata
- **Prospettive terapeutiche mediche**
  - Farmaci diretti su target genici
- **Nuovi geni nella oncogenesi**



Biologicamente differenti

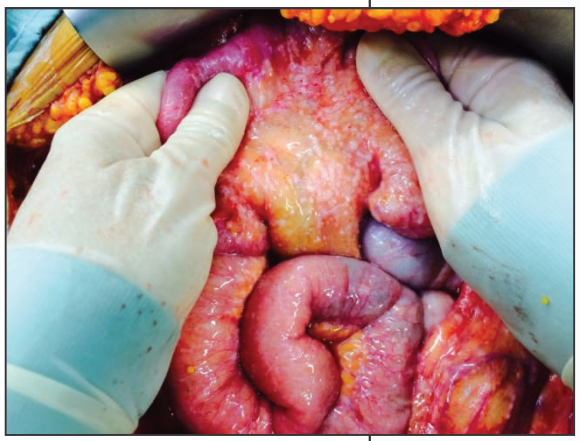
Vaughan et al Nat Rev Cancer (2011) 11:719

British Journal of Cancer (2011) 105, 1818 – 1824
© 2011 Cancer Research UK All rights reserved 0007 – 0920/11
www.bjcancer.com

Role of histological type on surgical outcome and survival following radical primary tumour debulking of epithelial ovarian, fallopian tube and peritoneal cancers

E-I Braicu[1], J Sehouli[1], R Richter[1], K Pietzner[1], C Denkert[2] and C Fotopoulou*,[1]

[1]European Competence Center for Ovarian Cancer Department of Gynecology, Charité, Campus-Virchow-Clinic/University-Hospital, Augustenburger Platz 1, Berlin 13353, Germany; [2]Institute of Pathology, Charité Hospital, University Medicine of Berlin, Berlin 13353, Germany



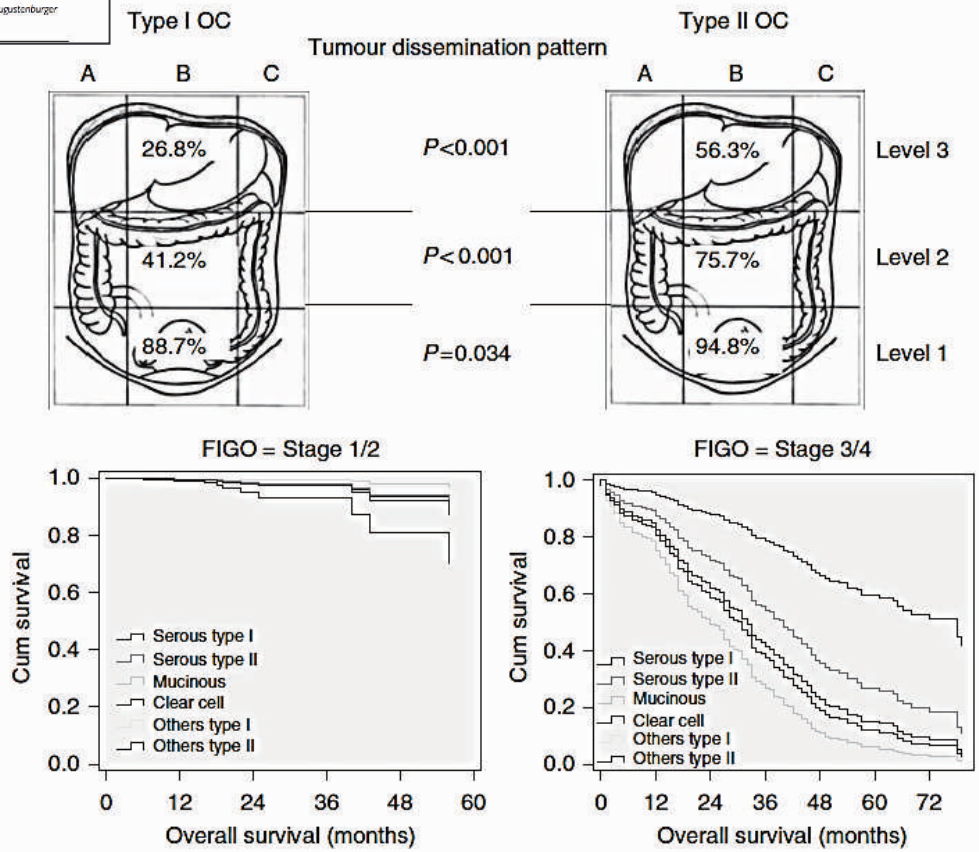
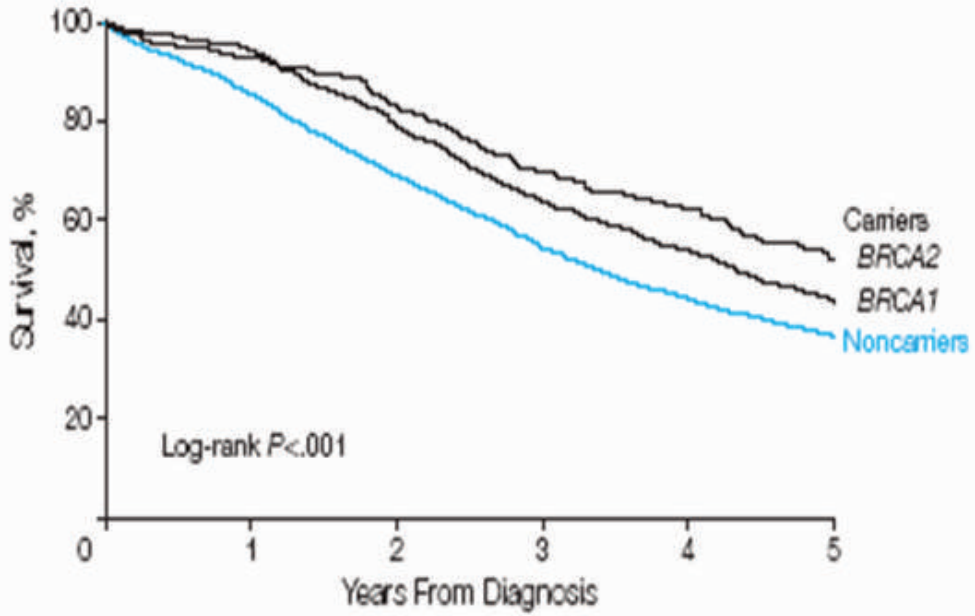


Figure 1 Tumour dissemination patterns in type I *vs* type II primary ovarian cancer (OC), according to the 'Intraoperative Mapping of Ovarian Cancer' documentation tool and survival curves according to histology depicted separately for FIGO (International Federation of Gynecology and Obstetrics) stages I/II and III/IV.

Impact for the patient prognosis

Figure. Kaplan-Meier Estimates of Cumulative Survival According to *BRCA1/2* Status



No. at risk

Pooled analysis of 26 observational studies

Bolton et al. JAMA 2012;307 (4):382-390

REVIEW ARTICLE

Int J Gynecol Cancer 2016

Minimal Macroscopic Residual Disease (0.1–1 cm). Is It Still a Surgical Goal in Advanced Ovarian Cancer?

Luis M. Chiva, MD, PhD, Teresa Castellanos, MD, Sonsoles Alonso, MD, and Antonio Gonzalez-Martin, MD

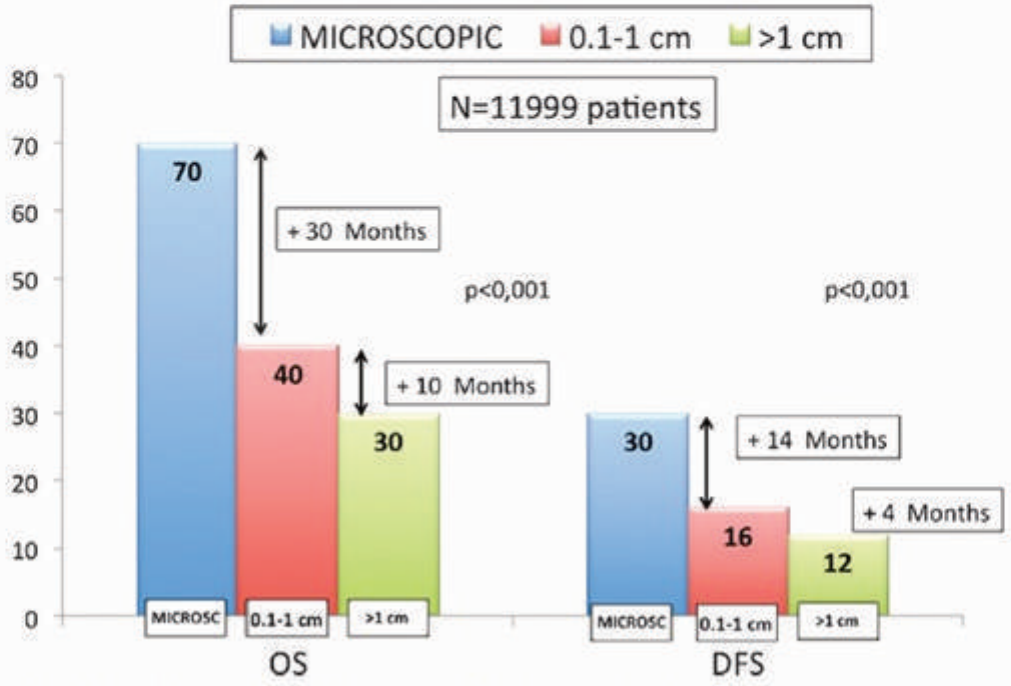
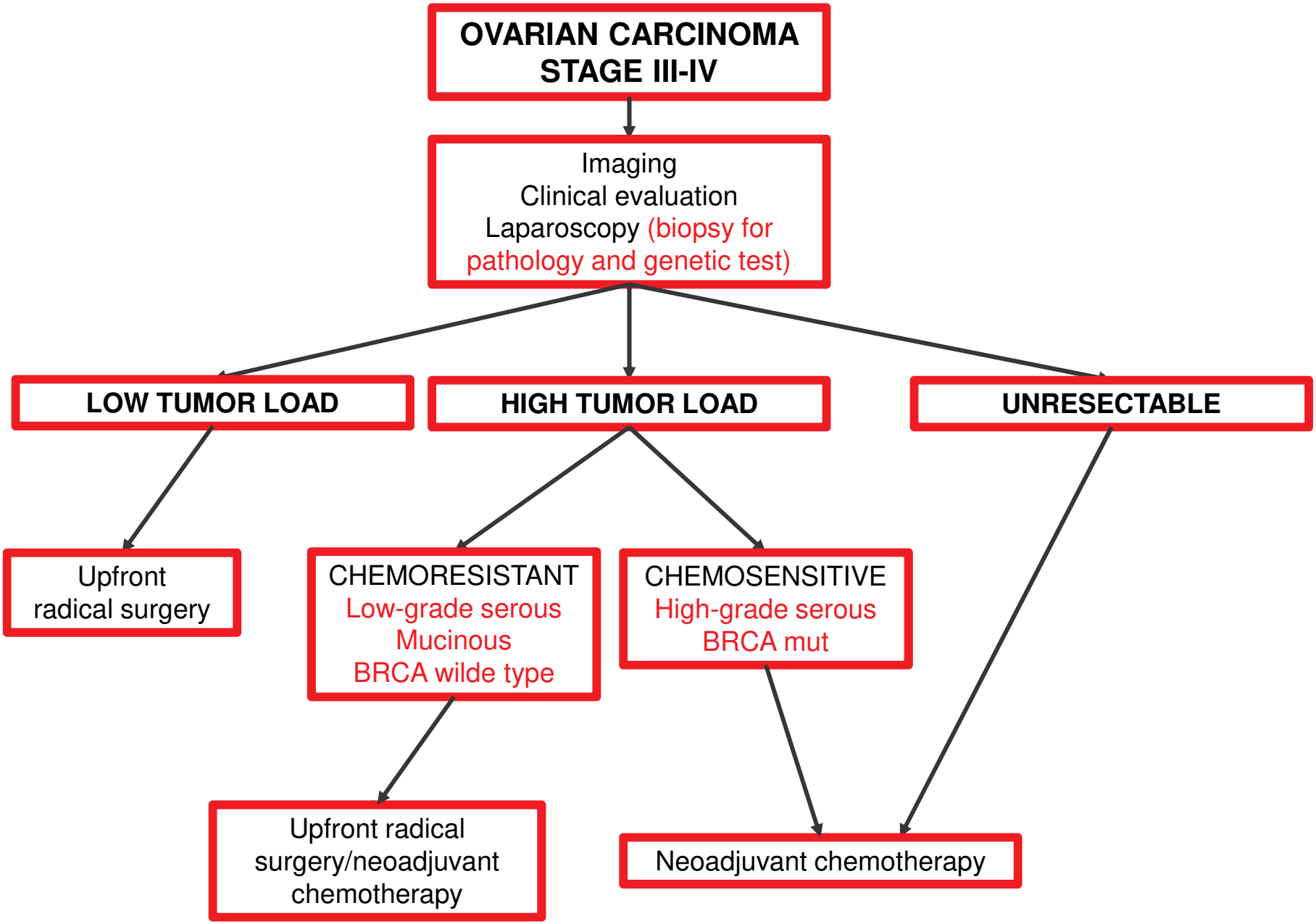


FIGURE 1. Differences in OS and DFS among groups depending on the amount of residual disease.


OVARIAN CARCINOMA
STAGE III-IV
Imaging
Clinical evaluation
Laparoscopy (biopsy for pathology and genetic test)
LOW TUMOR LOAD
HIGH TUMOR LOAD
UNRESECTABLE
Upfront radical surgery
CHEMORESISTANT
Low-grade serous
Mucinous
BRCA wilde type
CHEMOSENSITIVE
High-grade serous
BRCA mut
Upfront radical surgery/neoadjuvant chemotherapy
Neoadjuvant chemotherapy

GENETICA E ONCOLOGIA

- **Studio familiarità tumorale**
  - Screening per familiari
  - Chirurgia di riduzione del rischio
- **Studio pannello genetico del tumore**
  - Analisi cellule tumorali (somatico)
  - Analisi cellule germinali
- **Prospettive terapeutiche chirurgiche**
  - Chirurgia gene-modulata
- **Prospettive terapeutiche mediche**
  - Farmaci diretti su target genici
- **Nuovi geni nella oncogenesi**

Clinical Therapeutics/Volume 40, Number 3, 2018

Reviews

Use of Targeted Therapeutics in Epithelial Ovarian Cancer: A Review of Current Literature and Future Directions

Monica Hagan Vetter, MD[1]; and John L. Hays, MD, PhD[1,2]

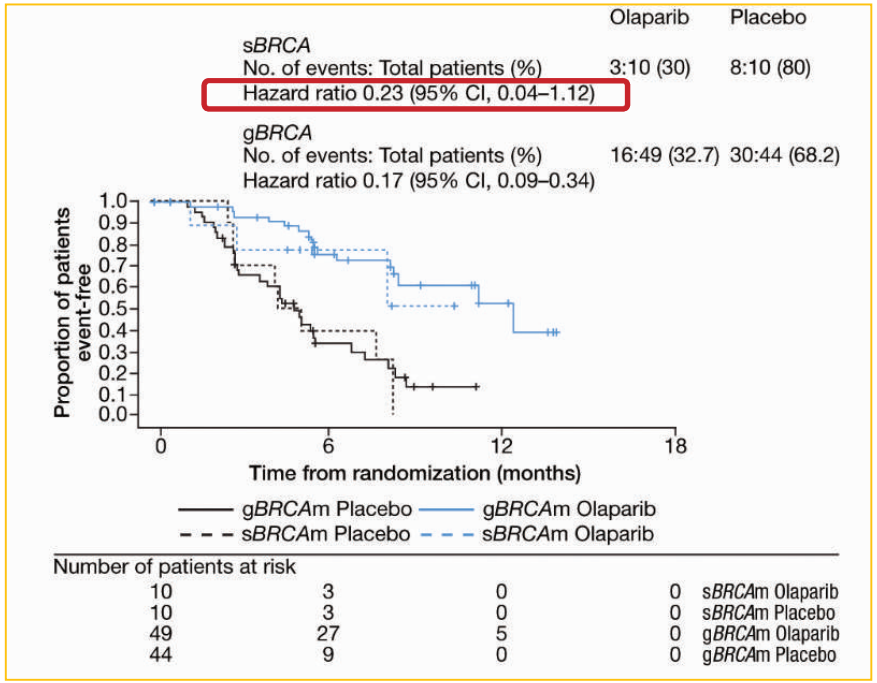
Table I. Clinical trials of targeted monotherapy that are currently recruiting, accessed September 1, 2017.

Study Identification	Title	Phase	Status
Antiangiogenics			
NCT02558348	Phase I/IIa Evaluation of AL3818 in Subjects With Recurrent or Metastatic Endometrial, Ovarian or Cervical Cancer (AL3818-US-001)	I/II	Recruiting
NCT01669798	BIBF 1120 in Bevacizumab Resistant, Persistent or Recurrent Epithelial EOC	II	Recruiting
PARP inhibitors			
NCT02354586	A Study of Niraparib in Patients With EOC Who Have Received Three or Four Previous Chemotherapy Regimens (QUADRA)	II	Recruiting
NCT02575651	A Phase I Study of Fluzoparib in Patients with Advanced Solid Malignancies	I	Recruiting
NCT02655016	A Study of Niraparib Maintenance Treatment in Patients with Advanced EOC Following Response on Front-Line Platinum-Based Chemotherapy	III	Recruiting
PI3K/AKT/mTOR inhibition			
NCT01226316	Safety, Tolerability and Potential Anti-cancer Activity of Increasing Doses of AZD5363 in Different Treatment Schedules	I	Recruiting
NCT02142803	TORC1/2 Inhibitor MLN0128 and Bevacizumab in Treating Patients With Recurrent Glioblastoma or Advanced Solid Tumors	I	Recruiting
NCT02646319	Nanoparticle Albumin-Bound Rapamycin in Treating Patients With Advanced Cancer With mTOR Mutations	II	Recruiting
MAPK pathway			
NCT02101788	Trametinib in Treating Patients With Recurrent or Progressive Low-Grade EOC or Peritoneal Cavity Cancer	II/III	Recruiting

BIBF 1120 = nintedanib; EOC = epithelial ovarian cancer; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; PARP = poly (ADP-ribose) polymerase; PI3K = phosphatidylinositol 3-kinase; TORC = target of rapamycin complex.

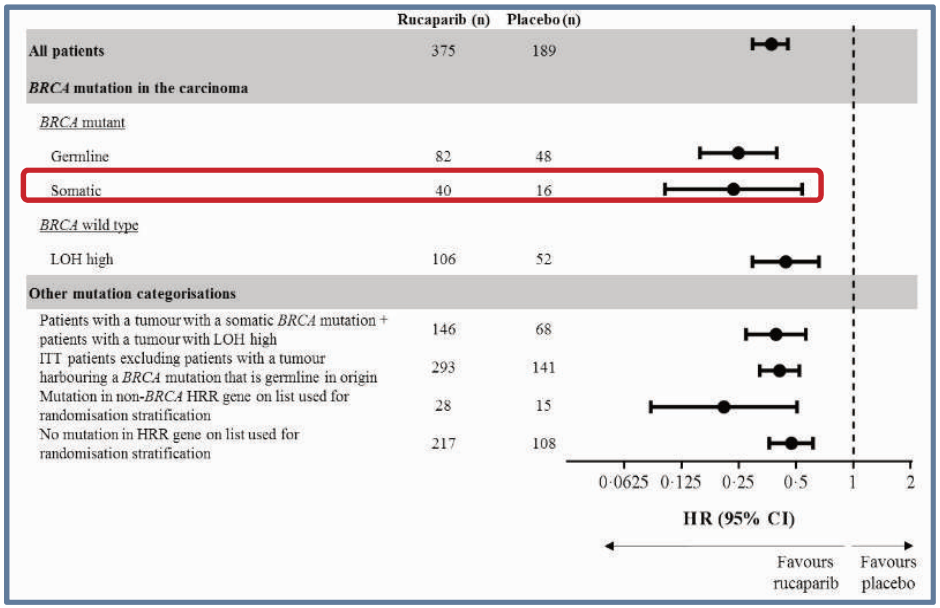
Non è dimostrato che le mutazioni somatiche abbiano lo stesso significato predittivo delle varianti costituzionali

Studio 19



Dougherty, Oncotarget, 2017

ARIEL 3



Coleman, Lancet, 2017

GENETICA E ONCOLOGIA

- **Studio familiarità tumorale**
  - Screening per familiari
  - Chirurgia di riduzione del rischio
- **Studio pannello genetico del tumore**
  - Analisi cellule tumorali (somatico)
  - Analisi cellule germinali
- **Prospettive terapeutiche chirurgiche**
  - Chirurgia gene-modulata
- **Prospettive terapeutiche mediche**
  - Farmaci diretti su target genici
- **Nuovi geni nella oncogenesi**

Girolimetti et al. Molecular Cancer (2017) 16:47
DOI 10.1186/s12943-017-0614-y

Molecular Cancer

LETTER TO THE EDITOR

Mitochondrial DNA sequencing demonstrates clonality of peritoneal implants of borderline ovarian tumors

Giulia Girolimetti[1], Pierandrea De Iaco[2], Martina Procaccini[2], Riccardo Panzacchi[3], Ivana Kurelac[1], Laura Benedetta Amato[1], Giulia Dondi[2], Giacomo Caprara[4], Claudio Ceccarelli[5], Donatella Santini[3], Anna Maria Porcelli[6], Anna Myriam Perrone[2†] and Giuseppe Gasparre[1*†]

Abstract

Borderline ovarian tumors are rare low malignant potential neoplasms characterized by the absence
invasion, whose main prognostic factors are stage and type of peritoneal implants. The latter are def
invasive when cell proliferation invades the underlying tissue (peritoneal surface, omentum and intes
or noninvasive. It is still unknown if these implants are metastatic spread from the primary ovarian m
neoplastic transformation *de novo* of the peritoneal surface. Mitochondrial DNA sequencing was perf
assess clonality in eight patients presenting both borderline ovarian tumors and implants. In 37.5% o
the same mitochondrial DNA mutation was present in both borderline ovarian tumors and the perit
being this evidence that implants may arise as a consequence of a spread from a single ovarian site.

Keywords: Gynecological cancer, Mitochondrial DNA mutations, Borderline ovarian tumors, Peritone

International Journal of *Molecular Sciences*

MDPI

Review

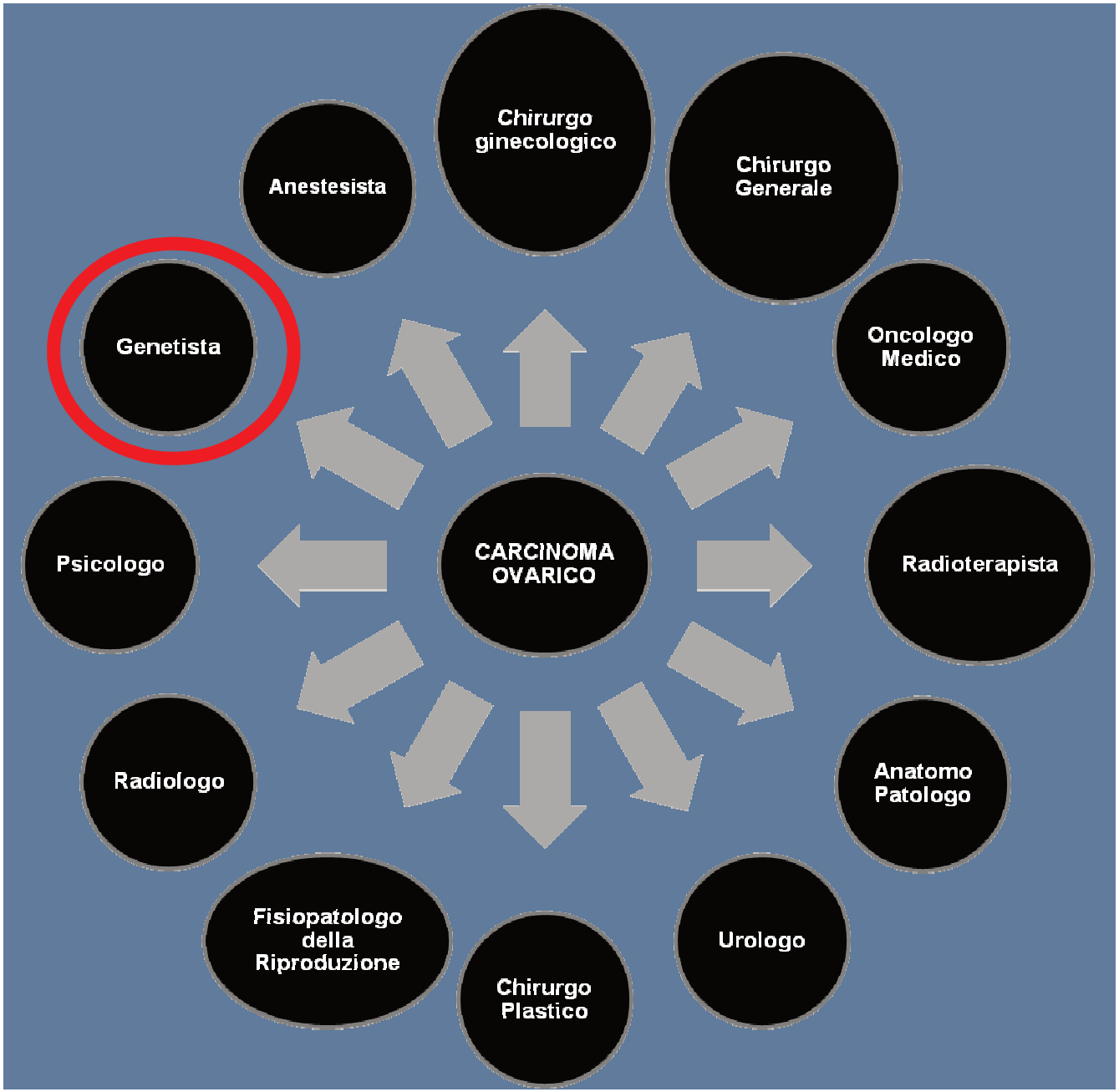
Potential for Mitochondrial DNA Sequencing in the Differential Diagnosis of Gynaecological Malignancies

Anna Myriam Perrone [1,*,†], Giulia Girolimetti [2,†], Martina Procaccini [1], Lorena Marchio [2], Alessandra Livi [1], Giulia Borghese [1], Anna Maria Porcelli [3], Pierandrea De Iaco [1] and Giuseppe Gasparre [2,4,*]

1 Unit of Oncologic Gynecology, Sant Orsola-Malpighi Hospital, via Massarenti 13, 40138 Bologna, Italy; martina.procaccini@gmail.com (M.P.); alessandra.livi2@studio.unibo.it (A.L.); giuliamaria.borghese@gmail.com (G.B.); pierandrea.deiaco@unibo.it (P.D.I.)
2 Unit of Medical Genetics, Department of Medical and Surgical Sciences (DIMEC), Sant Orsola Hospital, Pav.11, via Massarenti 9, 40138 Bologna, Italy; giulsgiuls85@gmail.com (G.G.); lorenamarchio@gmail.com (L.M.)
3 Department of Pharmacy and Biotechnology (FABIT), University of Bologna, 40138 Bologna, Italy; annamaria.porcelli@unibo.it
4 Center for Applied Biomedical Research (CRBA), University of Bologna, 40138 Bologna, Italy
* Correspondence: myriam.perrone@aosp.bo.it (A.M.P.); giuseppe.gasparre3@unibo.it (G.G.); Tel.:+39-051-214-4368 (A.M.P.); +39-051-208-8430 (G.G.); Fax: +39-051-636-4392 (A.M.P.); +39-051-208-8416 (G.G.)
† These authors contributed equally to this work.

Received: 22 May 2018; Accepted: 11 July 2018; Published: 13 July 2018

Abstract: In the event of multiple synchronous gynecological lesions, a fundamental piece of information to determine patient management, prognosis, and therapeutic regimen choice is whether the simultaneous malignancies arise independently or as a result of metastatic dissemination. An example of synchronous primary tumors of the female genital tract most frequently described are ovarian and endometrial cancers. Surgical findings and histopathological examination aimed at resolving this conundrum may be aided by molecular analyses, although they are too often inconclusive. High mitochondrial DNA (mtDNA) variability and its propensity to accumulate mutations has been proposed by our group as a tool to define clonality. We showed mtDNA sequencing to be informative in synchronous primary ovarian and endometrial cancer, detecting tumor-specific mutations in both lesions, ruling out independence of the two neoplasms, and indicating clonality. Furthermore, we tested this method in another frequent simultaneously detected gynecological lesion type, borderline ovarian cancer and their peritoneal implants, which may be monoclonal extra-ovarian metastases or polyclonal independent masses. The purpose of this review is to provide an update on the potential use of mtDNA sequencing in distinguishing independent and metastatic lesions in gynecological cancers, and to compare the efficiency of molecular analyses currently in use with this novel method.


Chirurgo ginecologico
Anestesista
Chirurgo Generale
Genetista
Oncologo Medico
Psicologo
CARCINOMA OVARICO
Radioterapista
Radiologo
Anatomo Patologo
Fisiopatologo della Riproduzione
Chirurgo Plastico
Urologo


Grazie