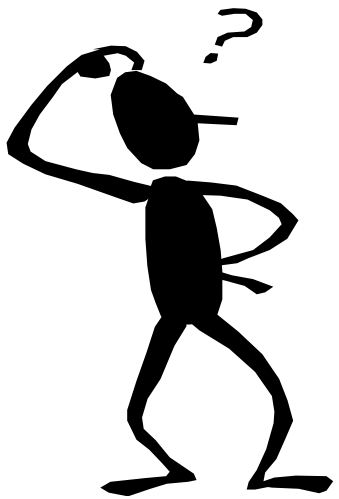
Raccomandazioni del Genetista

Dott.ssa Raffaella Casolino - Oncologia Negrar

Genetic Test and Ovarian Cancer



International Recomandations for BRCA Genetic Test

- **NCCN** (National Comprehensive Cancer Network):

Epithelial ovarian cancer at any age

- **Australian national guidelines:**

Women ≤70 years of age with ovarian cancer can receive genetic testing for *BRCA 1/2* mutations regardless of family history

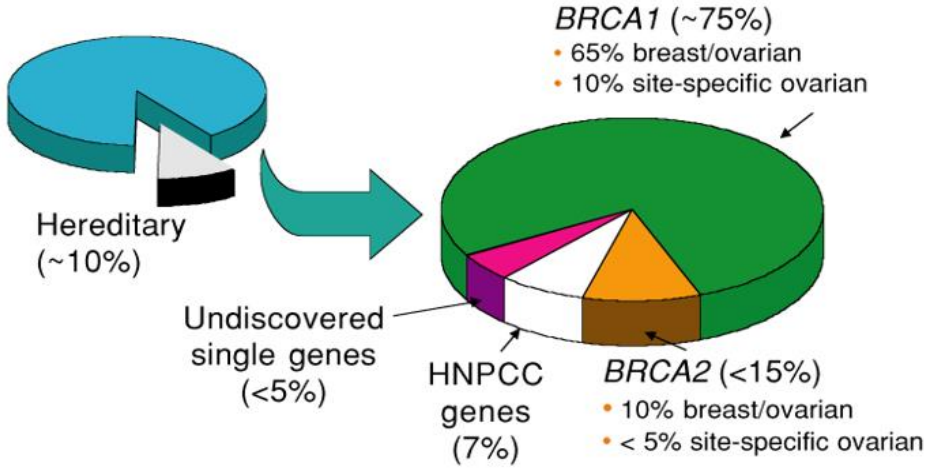
- **SGO** (Society of Gynecologic Oncology):

Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should be considered for genetic counseling and testing, even in the absence of a family history

- **Europe:**

No standardised guidelines, vary by country

An evolving paradigm: Yesterday



BRCA and Cancer

Although the risk of cancer is greater for women than men with BRCA 1/2 gene mutations, both sexes face elevated lifetime chances of several types of cancer. *Risk of cancer as a percentage, by gender.*

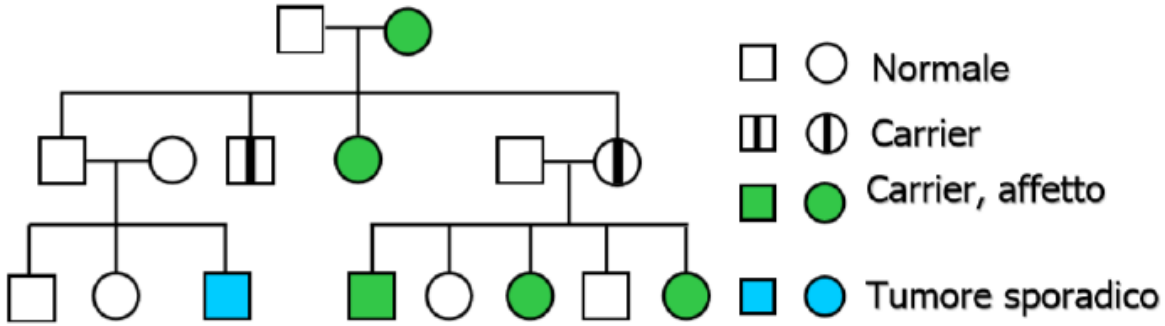
Cancer type	U.S. white	BRCA1 mutation carriers	BRCA2 mutation carriers
MEN			
Breast	0.1%	1-5%	7%
Prostate	16	*	25
Melanoma	2	N.S.	5
Pancreas	1	Up to 3	3-5
WOMEN			
Breast	13%	60-80%	50-70%
Ovary	1-2	20-45	10-20
Melanoma	2	N.S.	Up to 5
Pancreas	1	Up to 3	3-5

N.S. = Not significant; *Some evidence of an increased risk for men younger than 65

SOURCE: Penn Medicine's Basser Research Center for BRCA

MIKE PLACENTRA / Staff Artist

AD transmission – Incomplete penetrance



What were The Reasons To Undergo BRCA Genetic Test? Yesterday

- **Cancer risk reducing**

Screening

Lifestyle modification

Risk-reducing surgery

Risk-reducing agents

→ ***Preventive Role***

- Identification of **unaffected mutation carriers**

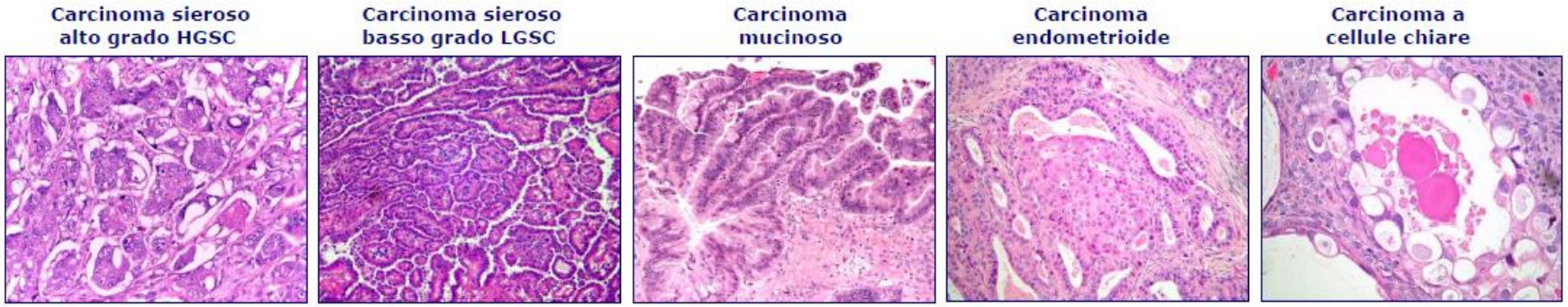
Family screening and prevention

An evolving paradigm: Today

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

Jaime Prat

Virchows Arch (2012) 460:237–249



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

HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma; CCC, clear-cell carcinoma.

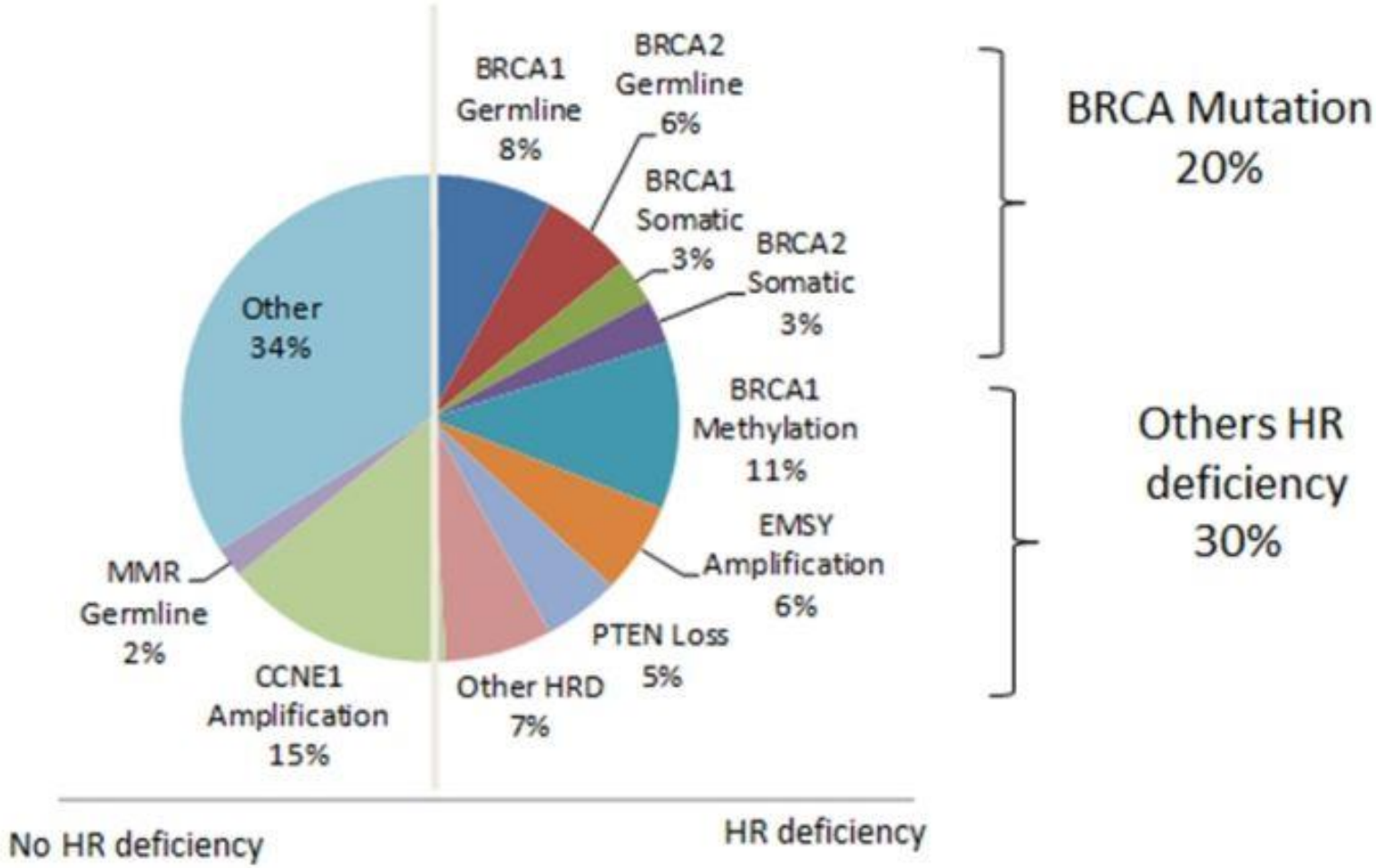
[a]Hereditary nonpolyposis colorectal carcinoma.

Courtesy of Anna Pesci

An evolving paradigm: Today

- > 10% of unselected ovarian cancer patients harbor a mutation in BRCA 1-2 genes
- 17-20% in serous ovarian carcinoma
- 25-30% of those with high grade serous histology have a BRCA mutation
- 30-40% platinum sensitive patients
- Up to 50% of high grade serous and endometrioid tumors present a malfunctioning of HR

High grade serous muellerian cancer is a disease of homologous recombination dysfunction



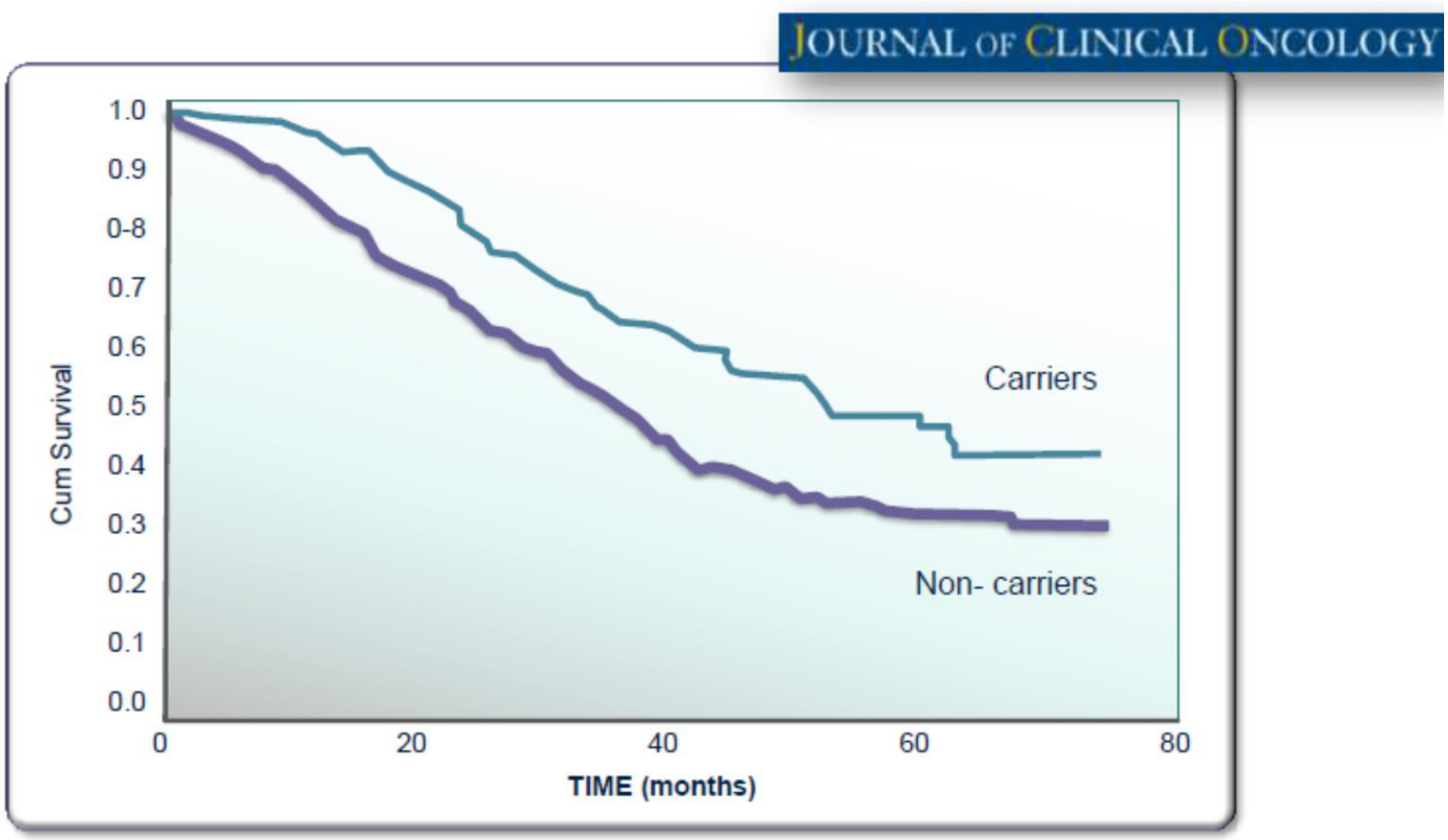
Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615

Is family history a predictor for a BRCA mutation?

Absence of family history among BRCA mutation carriers	
Walsh et al	30%
Jacobi et al	20%
Alsop et al	44%
Malander et al	10%
Soegaard et al	54%
Risch et al	20%

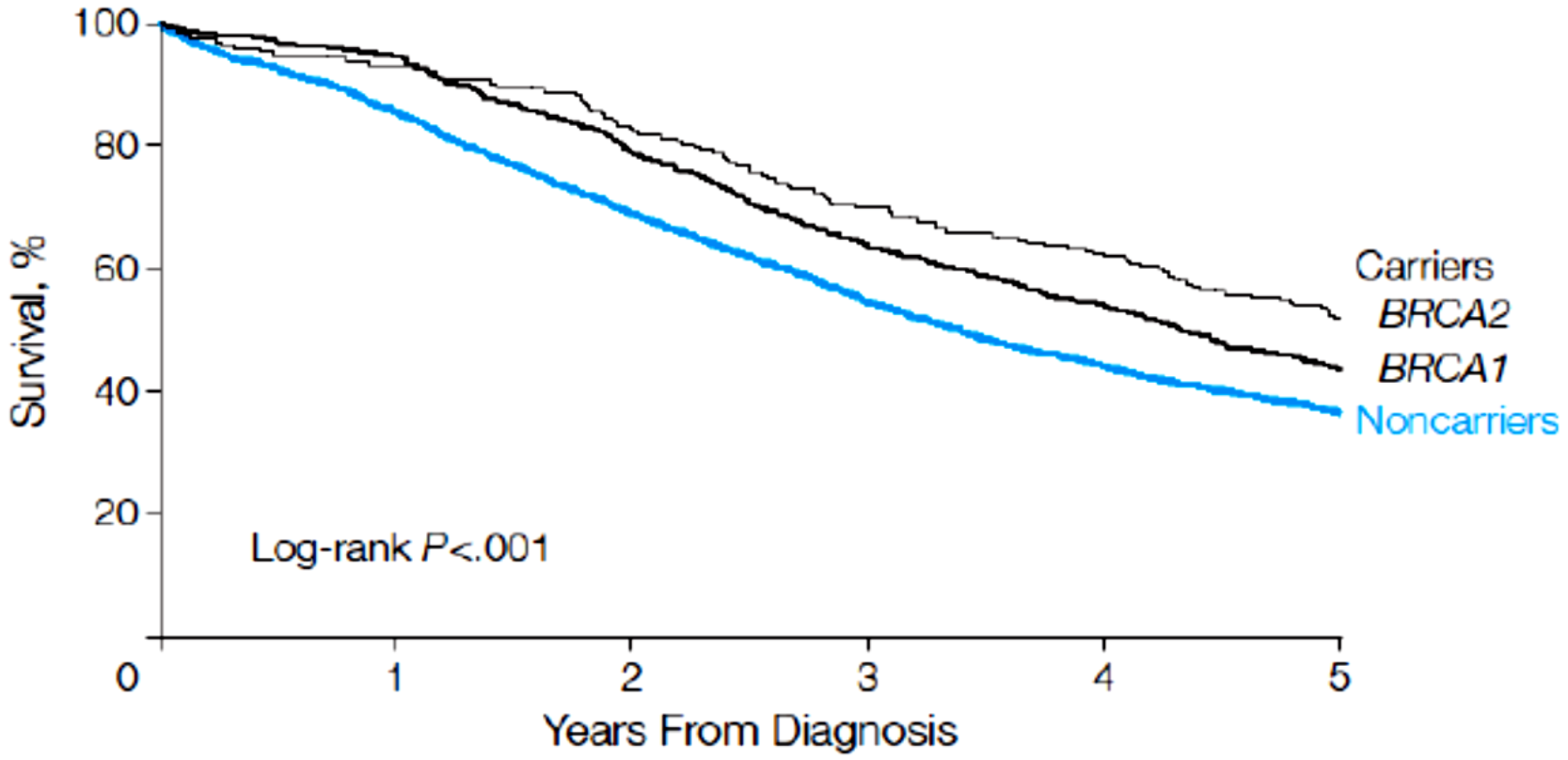
Approximately 30% of BRCA mutation carriers do not have a family history!

Prognostic relevance of BRCA mutation in Ovarian Cancer



Ben David Y et al. JCO 2002;20:463-6 by American Society of Clinical Oncology

Prognostic relevance of BRCA mutation in Ovarian Cancer

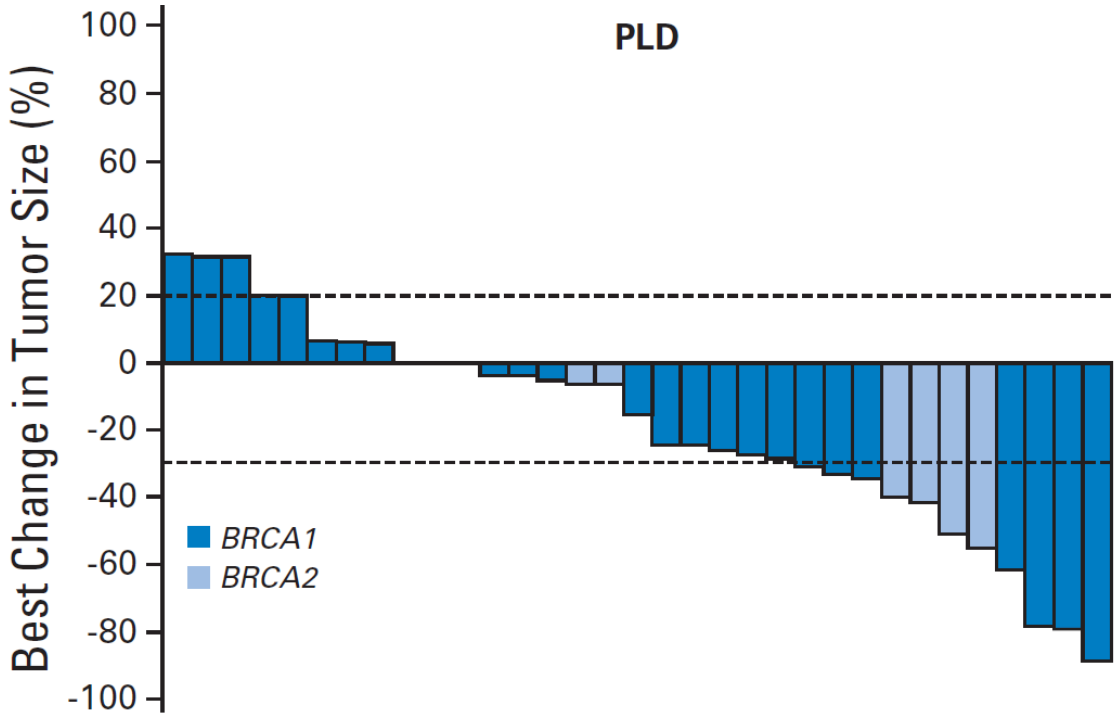


No. at risk						
Noncarriers	1047	1687	1540	1395	1225	1044
Carriers						
BRCA1	327	593	569	490	408	342
BRCA2	117	199	192	179	164	125

Bolton, JAMA 2012

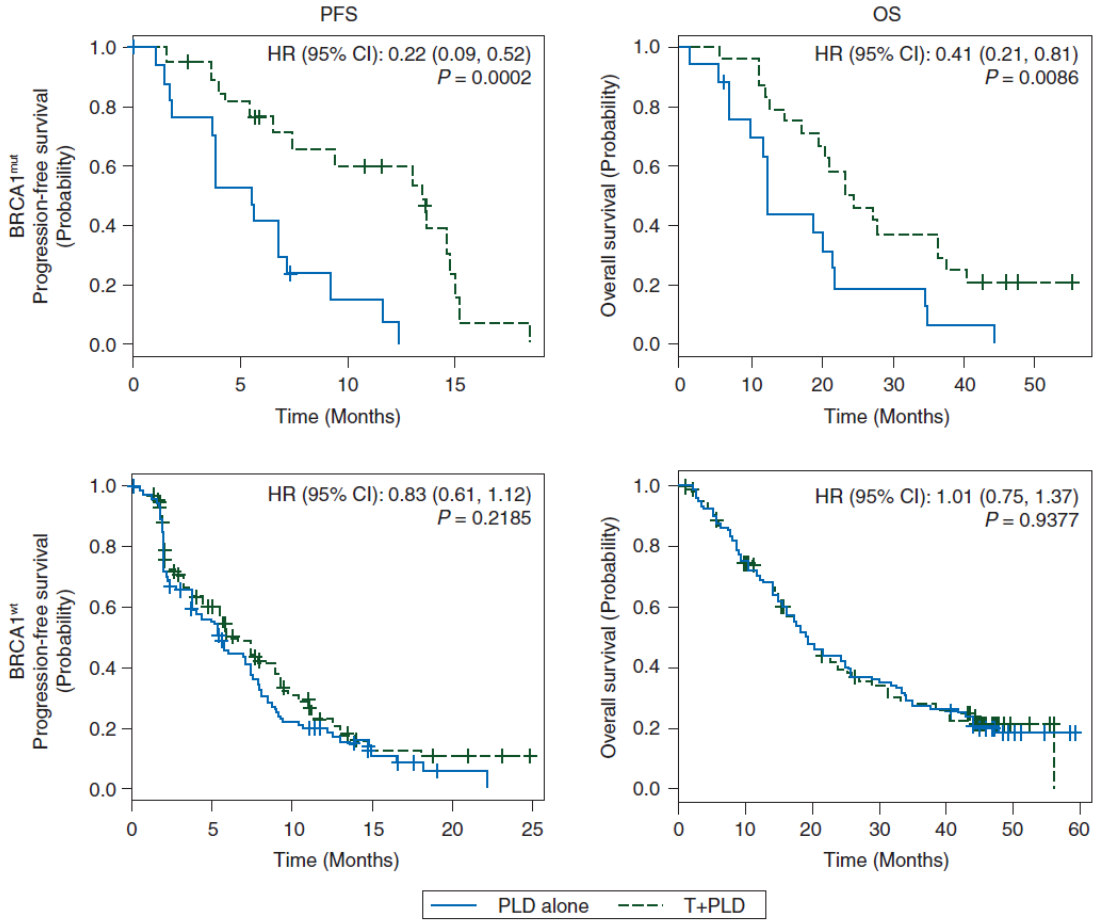
BRCA status and response to chemotherapy

- 42% platinum resistant; 58% partially platinum sensitive



Kaye SB, et al. J Clin Oncol 2012

- OVA-301 phase III study in recurrent ovarian cancer
- PLD +/- trabectedin



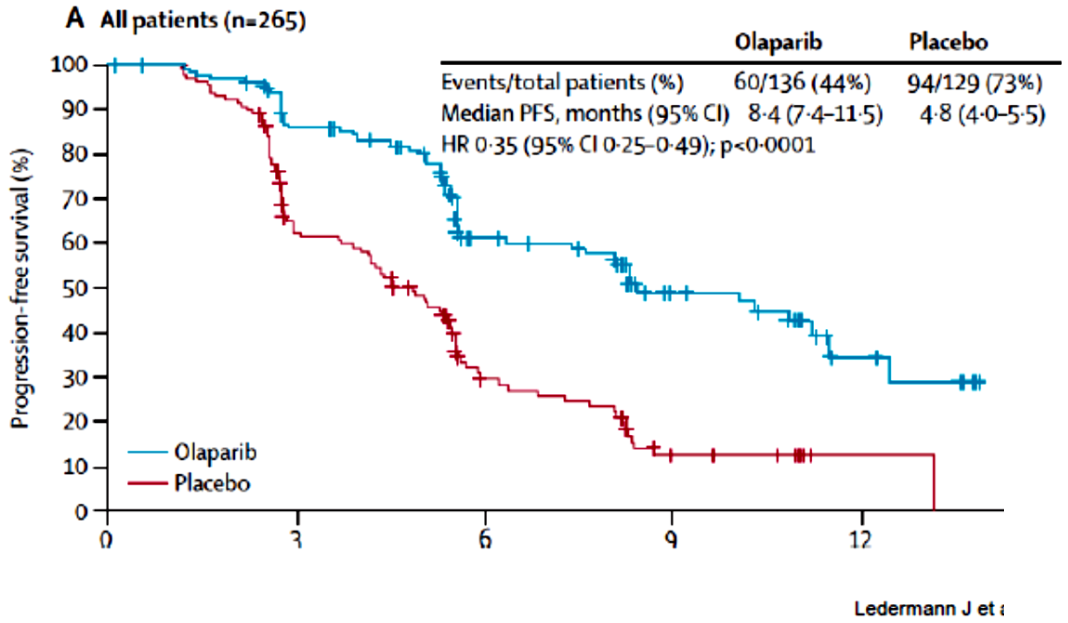
Monk , et al. Ann Oncol 2015

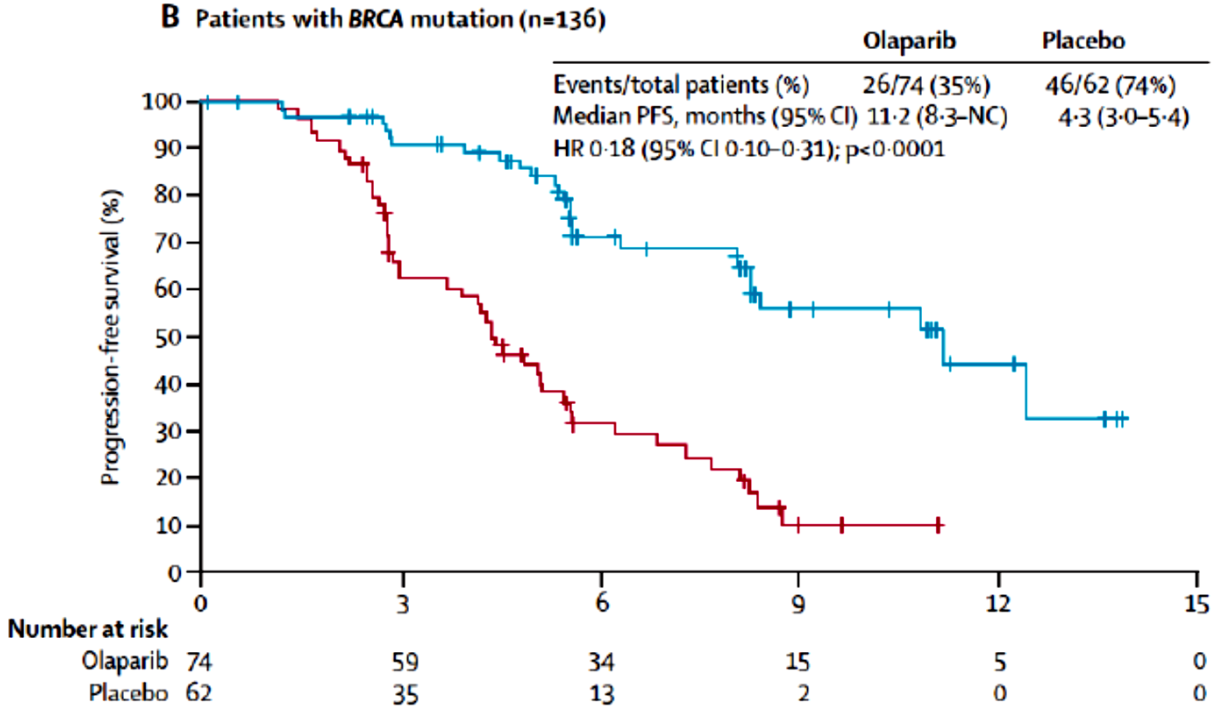
Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial

Lancet Oncol 2014; 15: 852–61

Predictive Biomarker

22% mBRCA
14% BRCA neg
63% BRCA unknown





What Are The Reasons To Undergo BRCA Genetic Test? Today

- Cancer risk reducing
- Identification of unaffected mutation carriers → ***Preventive***
- Prognostic relevance → ***Prognostic***
- Impact on patient treatment
  - Platinum sensitivity
  - Sensitivity to other chemotherapy
    - Pegylated liposomal doxorubicin
    - Trabectedin
  - Sensitivity to intraperitoneal chemotherapy
  - **PARP inhibition** → ***Predictive***

Raccomandazioni per l'implementazione del test BRCA nei percorsi assistenziali e terapeutici delle pazienti con carcinoma ovarico

A cura del Gruppo di Lavoro AIOM - SIGU - SIBIOC - SIAPEC-IAP

Maria Angela Bella, Ettore Capoluongo, Paola Carrera, Claudio Clemente, Nicoletta Colombo, Laura Cortesi, Gaetano De Rosa, Maurizio Genuardi, Stefania Gori, Valentina Guarneri, Antonio Marchetti, Paolo Marchetti, Nicola Normanno, Barbara Pasini, Sandro Pignata, Carmine Pinto, Paolo Radice, Enrico Ricevuto, Antonio Russo, Pierosandro Tagliaferri, Pierfrancesco Tassone, Mauro Truini, Liliana Varesco

Luglio 2015

Future ONCOLOGY

COMMENTARY

For reprint orders, please contact: reprints@futuremedicine.com

Recommendations for the implementation of *BRCA* testing in the care and treatment pathways of ovarian cancer patients

Carmine Pinto*[,1], Maria Angela Bella[2], Ettore Capoluongo[3], Paola Carrera[4], Claudio Clemente[5], Nicoletta Colombo[6], Laura Cortesi[7], Gaetano De Rosa[8], Francesca Fenizia[9], Maurizio Genuardi[10], Stefania Gori[11], Valentina Guarneri[12], Antonio Marchetti[13], Paolo Marchetti[14], Nicola Normanno[15], Barbara Pasini[16], Sandro Pignata[17], Paolo Radice[18], Enrico Ricevuto[19], Antonio Russo[20], Pierosandro Tagliaferri[21], Pierfrancesco Tassone[21,22], Mauro Truini[23] & Liliana Varesco[24]

First submitted: 13 April 2016; Accepted for publication: 10 May 2016; Published online: 31 May 2016

" E' consigliabile considerare l'invio al test BRCA, <u>sin dal momento della diagnosi</u> :

- ***Carcinoma epiteliale ovarico non mucinoso e non borderline***
- ***Carcinoma delle tube di Falloppio***
- ***Carcinoma peritoneale primitivo***

per completare la fase diagnostica molecolare e per la pianificazione del trattamento"

Types of BRCA testing

Germline mutations (2/3)→ Peripheral blood

-Sanger

-Next Generation Sequencing (under validation)

Somatic mutations (1/3)→ Tumor tissue

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 2

BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing

Andrea Mafficini[1,*], Michele Simbolo[1,*], Alice Parisi[2], Borislav Rusev[1,2], Claudio Luchini[1,2], Ivana Cataldo[1], Elena Piazzola[2], Nicola Sperandio[1], Giona Turri[2], Massimo Franchi[3], Giampaolo Tortora[4], Chiara Bovo[5], Rita T. Lawlor[1,2] and Aldo Scarpa[1,2]

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[*] Shared first authors

Table 1: Pathogenic mutations in *BRCA1* and *BRCA2* detected by next-generation sequencing of 47 ovarian cancers.

Case	*BRCA1*	*BRCA2*	Mutation type	Germline-somatic	dbSNP ID	ClinVar class
3506	c.5329dupC p.Gln1777ProfsTer74	-	Frameshift	Germline	rs397507247	Pathogenic
3513	c.676delT p.Cys226ValfsTer8	-	Frameshift	Germline	rs80357941	Pathogenic
3508	c.1687C>T p.Gln563Ter	-	Nonsense	Germline	rs80356898	Pathogenic
3521	c.2405_2406delTG p.Val802GlufsTer7	-	Frameshift	Germline	rs80357706	Pathogenic
3528	c.2405_2406delTG p.Val802GlufsTer7	-	Frameshift	Germline	rs80357706	Pathogenic
3489	c.3767_3768delCA p.Thr1256ArgfsTer10	-	Frameshift	Germline	rs730881440	Pathogenic
3505	c.5125_5127delGTT p.Val1709del	-	In-frame deletion	Germline	rs80358344	Pathogenic
3520	c.5309C>T p.Pro1770Leu	-	Missense	Germline	-	-*
3512	-	c.2813delC p.Ala938GlufsTer22	Frameshift	Somatic	-	-**
3523	-	c.6202dupA p.Ile2068AsnfsTer10	Frameshift	Germline	rs397507833	Pathogenic
3514	-	c.6574delA p.Met2192TrpfsTer14	Frameshift	Germline	-	-**
3501	-	c.7069_7070delCT p.Leu2357ValfsTer2	Frameshift	Somatic	rs80359636	Pathogenic
3516	-	c.8614G>T p.Glu2872Ter	Nonsense	Somatic	-	-**

Results from Genetic Testing

Positive

Deleterious mutation identified

Negative

Interpretation differs if a mutation has previously been identified in the family

- Mutation known – true negative
- Mutation unknown – uninformative

Variant of unknown significance (VUS)

Significance will depend on how variant tracks through family - i.e. is variant present in people with disease?

Can use software to predict functional significance

Check with lab to see if reported previously

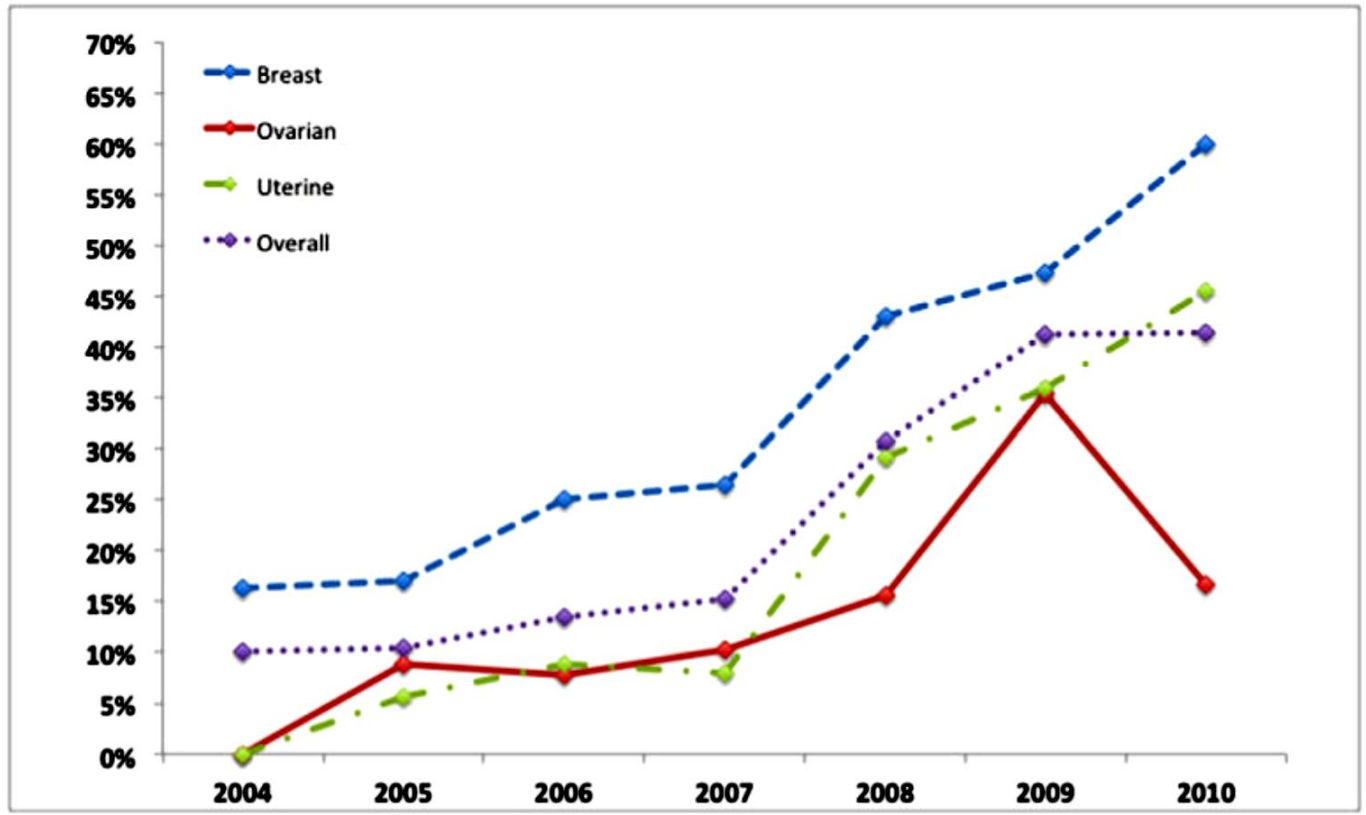
IARC 5-tier classification: Interpretation of *BRCA genetic variants*

Class	Description	Probability of being pathogenic	Clinical predictive testing of at risk relatives	Management recommendations if at-risk relative has the variant	Research testing of family members
5	**Definitely pathogenic**	>0.99	Yes	Full high-risk guidelines	Not indicated
4	**Likely pathogenic**	0.95-0.99	Yes	Full high-risk guidelines	May be helpful to further classify variant
3	**Uncertain**	0.05-0.949	No	Presence of variant is irrelevant to risk assessment, manage risk based on family history only	May be helpful to further classify variant
2	**Likely not pathogenic or of no clinical significance**	0.001-0.049	No	Manage risk based on family history only	May be helpful to further classify variant
1	**Not pathogenic or of no clinical significance**	<0.001	No	Manage risk based on family history only	Not indicated

Modified from Plon et al, Hum Mutat.2008

Adherence patterns to National Comprehensive Cancer Network (NCCN) guidelines for referral to cancer genetic professionals

Terri Febbraro[a,*,1], Katina Robison[a,b], Jennifer Scalia Wilbur[a,b], Jessica Laprise[a,b], Amy Bregar[a], Vrishali Lopes[a,c], Robert Legare[a,b], and Ashley Stuckey[a,b]



	2004	2005	2006	2007	2008	2009	2010
Breast	16.3%	17.1%	25.0%	26.5%	43.1%	47.3%	60.0%
Ovarian	0.0%	8.9%	7.7%	10.3%	15.6%	35.3%	16.7%
Uterine	0.0%	5.7%	8.8%	7.9%	29.2%	36.0%	45.5%
Overall	10.0%	10.4%	13.5%	15.2%	30.7%	41.2%	41.5%

Gynecol Oncol. 2015 July ; 138(1): 109–114.

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

The Angelina effect: immediate reach, grasp, and impact of going public

Dina L.G. Borzekowski, EdD[1], Yue Guan, ScM[2], Katherine C. Smith, PhD[2], Lori H. Erby, PhD[2] and Debra L. Roter, DrPH[2]

Background: In May 2013, Angelina Jolie revealed in a *New York Times* opinion piece that she had undergone a preventive double mastectomy because she had a family history of cancer and carried a rare mutation of the *BRCA1* gene. Media coverage has been extensive, but it is not obvious what messages the public took from this personal health story.

Methods: We conducted a survey with a representative national online panel of 2,572 adults. Participants described their awareness and identified information sources for the Angelina Jolie news story. They also reported their understanding, reactions, perceptions, and subsequent activities related to the story. We asked questions pertaining to personal and societal breast cancer risk and hypothetical questions regarding preventive surgery if the respondent or a family member were in the same position as Ms Jolie. Demographic information was collected, as was family risk for breast and ovarian cancer, and a gauge of numeracy.

Results: While three of four Americans were aware of Angelina Jolie's double mastectomy, fewer than 10% of respondents had the information necessary to accurately interpret Ms Jolie's risk of developing cancer relative to a woman unaffected by the *BRCA* gene mutation. Awareness of the Angelina Jolie story was not associated with improved understanding.

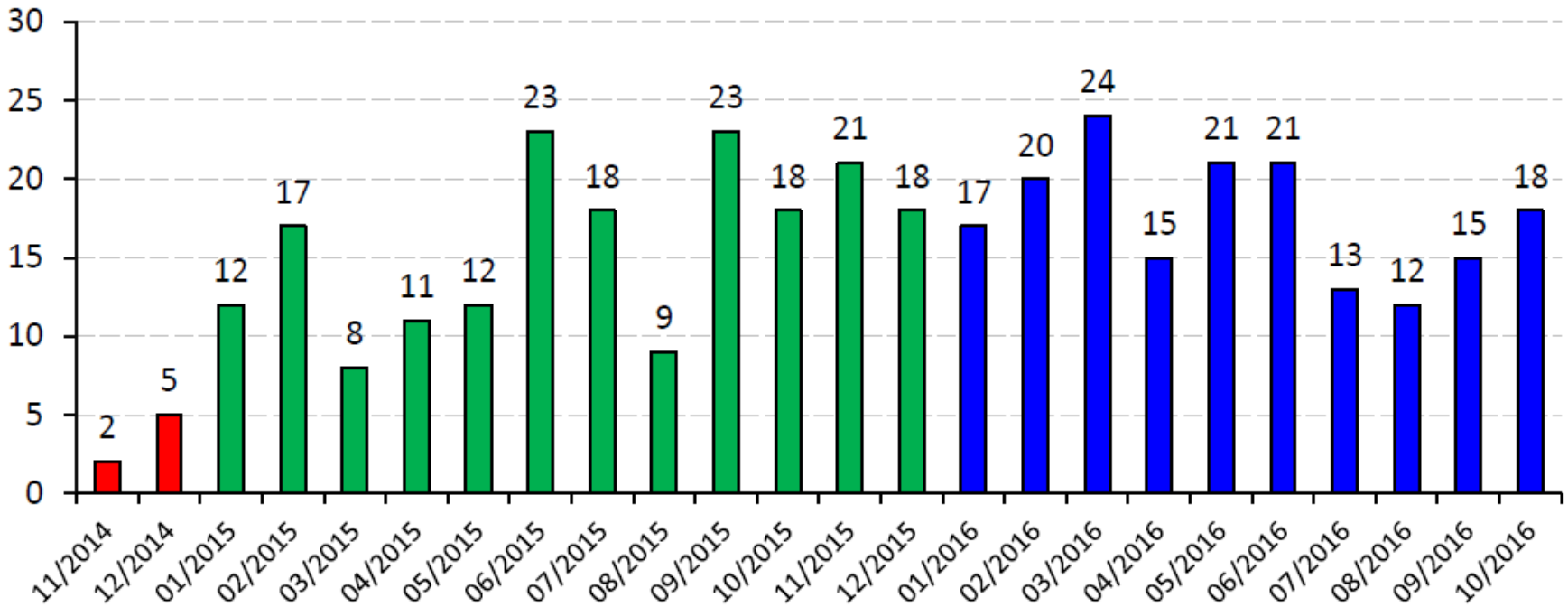
Conclusion: While celebrities can bring heightened awareness to health issues, there is a need for these messages to be accompanied by more purposeful communication efforts to assist the public in understanding and using the complex diagnostic and treatment information that these stories convey.

Genet Med advance online publication 19 December 2013

Key Words: breast cancer; celebrity health narratives; *BRAC1/2*; health communication

Ambulatorio Counseling genetico
Dipartimento Oncologia

- Andamento mensile:



- Riepilogo annuale

2014 (01/11 – 31/12)	2015	2016 (01/01 – 31/10)
7	190	176

Ambulatorio Counseling genetico
Dipartimento Oncologia

- Riepilogo annuale

	2015 (01/06 – 31/12)			**2016** (01/01 – 31/10)		
	Pts ca mammella	**Pts ca ovaio**	**Totale**	**Pts ca mammella**	**Pts ca ovaio**	**Totale**
Prelievi effettuati	23	21	**44**	38	32	**70**
Risultati pervenuti	6	14	**20**	14	8	**22**
Mutazione BRCA 1/2	3	3	**6**	0	3	**3**

Conclusions

• Consider offering the test **at the time of initial diagnosis** to all patients with:
-Nonmucinous and nonborderline ovarian epithelial carcinoma
-Fallopian tube carcinoma
-Primary peritoneal carcinoma

•BRCA mutations represent a **biomarker predictive** of sensitivity to treatment with PARP inhibitors, in addition to cancer risk assessment

•The use of BRCA testing as a treatment decision tool implies that it should be **readily accessible** to all those patients who may benefit from it and that the test results be made available within a **time compatible with the clinical needs**

•The **timing** of BRCA testing should be chosen with the patient in order to respect her needs for the decision-making process

• Importance of genetic counseling (family screening and prevention)

•Final goal: to improve the outcome of therapy, to promote prevention and finally to reduce mortality of ovarian cancer.

Grazie!

Sacro Cuore
Don Calabria
CCC
Cancer Care Center
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Sacro Cuore -Don Calabria CANCER CARE CENTER

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