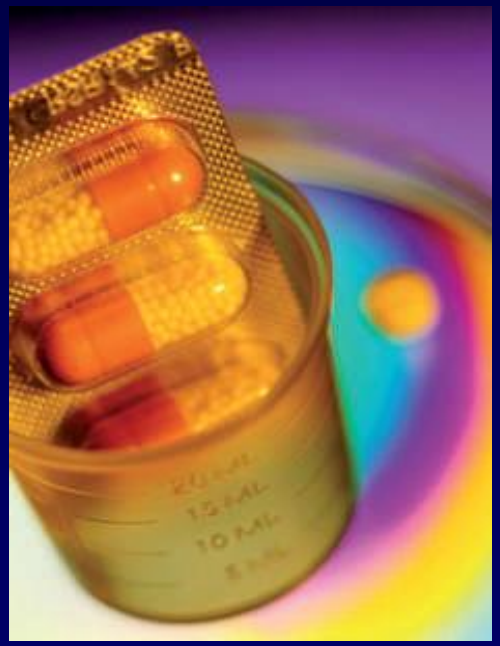
Advanced Ovarian Cancer: Why Should I Recommend *BRCA* Testing?

Judith Balmaña, MD, PhD
Familial Cancer Program
University Hospital Vall d'Hebron
Barcelona, Spain

What Are the Reasons to Undergo *BRCA* Genetic Testing?

Risk assessment



Therapeutic decision-making

Prophylactic surgery

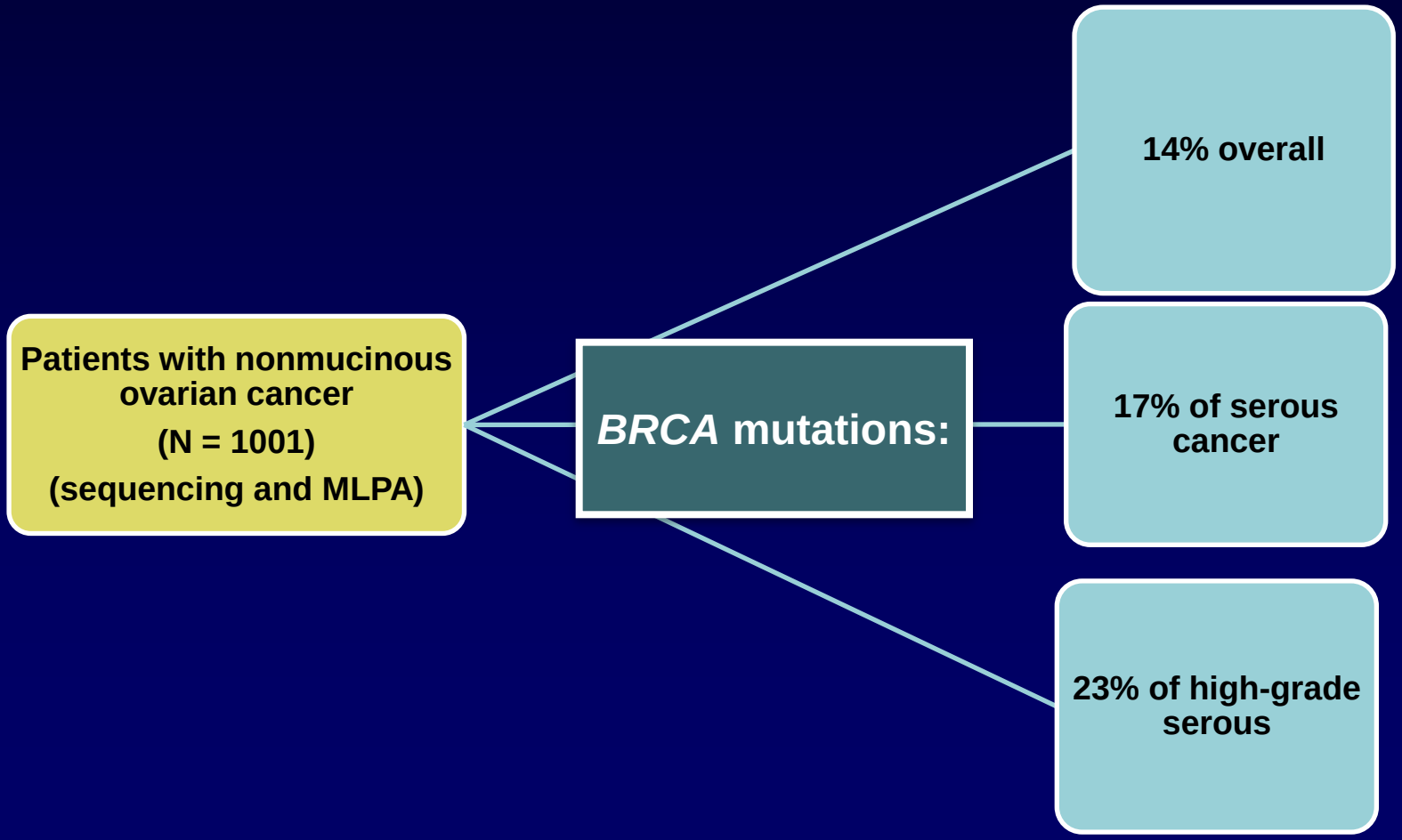
Systemic therapies

Prevalence of *BRCA* Mutations in Unselected Patients With Ovarian Cancer

Study	Population	Main Features	*BRCA1/2* Frequency
Hirsh-Yechezkel, 2003 (Israel)[1]	896 3 founder mutations	779 invasive 117 borderline	29% 4% (similar to the rate in the general Israeli population)
Risch, 2006 (Ontario, Canada)[2]	1171 PTT and DHPLC	977 invasive 194 borderline	Overall 13% Serous 18% Endometrioid/clear cell 7% Borderline/Mucinous 0%
Malander , 2004 (Southern Sweden)[3]	161 PTT and DHPLC	All invasive Borderline excluded	Overall 8% Serous 8% Endometrioid 13% Mucinous 0%
Soegaard, 2008 (Denmark)[4]	445 Sequencing and MLPA	All Invasive Borderline excluded	Overall 6% Serous 5.4% Endometriod 5.4% Clear cell 9% Mucinous 0%

1. Hirsh-Yechezkel G, et al. *Gynecol Oncol.* 2003;89(3):494-498. 2. Risch HA, et al. *J Natl Cancer Inst.* 2006;98(23): 1694-1706. 3. Malander S, et al. *Eur J Cancer.* 2004;40(3):422-428. 4. Soegaard M, et al. *Clin Cancer Rev.* 2008;14(12): 3761-3767.

Australian Population-Based Study of *BRCA* Mutation in Patients With Ovarian Cancer



Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663.

BRCA1/2 Germline Mutations Were Not Limited to High-Grade Serous Cancer

Endometrioid ovarian carcinoma (EC)

BRCA mutations in **8.4%**

(10/119 women)

Clear cell carcinoma (CCC) or mixed CCC/serous

BRCA mutations in **6%**

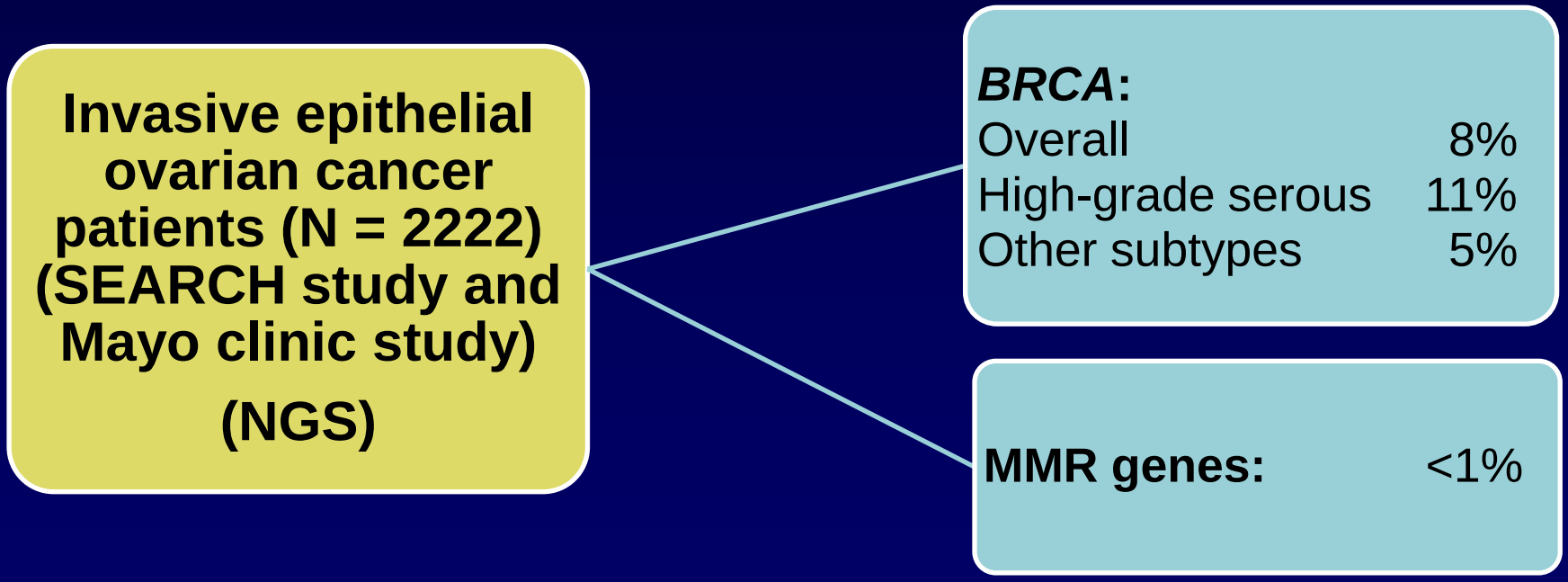
(4/63 women)

Carcinosarcomas

No patients (out of 34) identified as having *BRCA* mutation

Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663.

Mutation in *BRCA* (and *MMR* Genes) Among Patients With Ovarian Cancer in the Population



Song H, et al. *Hum Mol Genet.* 2014;23(17):4703-4709.

Is Age at Diagnosis a Predictor of a *BRCA* Mutation?

	BRCA1/2 -	*BRCA1 +*	*BRCA2 +*
Alsop et al	60y	53 y	60 y
Soegaard et al	61 y	49 y	
Risch et al	56 y	51 y	57 y
Malander et al	59 y	57 y	
Song et al	59 y	52y	57y

Approximately 25% of *BRCA1/2* mutation carriers are older than 60 years

Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663. Soegaard M, et al. *Clin Cancer Rev.* 2008;14(12):3761-3767. Risch HA, et al. *J Natl Cancer Inst.* 2006;98(23):1694-1706. Malander S, et al. *Eur J Cancer.* 2004;40(3):422-428. Song H, et al. *Hum Mol Genet.* 2014;23(17):4703-4709.

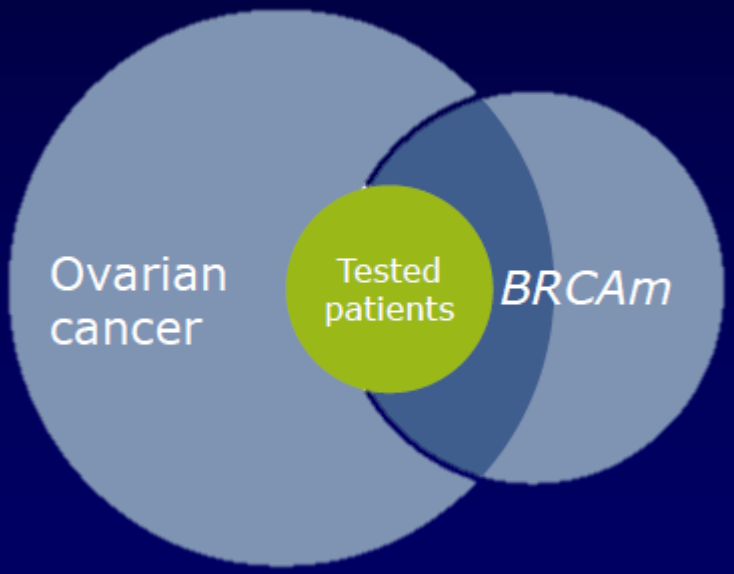
Is Family History a Predictor of a *BRCA* Mutation?

	Frequency of *BRCA* in the Presence of Family History	Frequency of *BRCA* in the Absence of Family History	Percentage of *BRCA* Mutation Carriers Who Lack a Family History
Walsh et al	29%	8%	27%
Soegaard et al	27%	3.5%	54%
Malander et al	92%	0%	8%
Risch et al	34%	5%	37%
Alsop et al	39%	8%	44%
Song et al	19%	5%	39%

Approximately 35% of *BRCA1/2* mutation carriers do not have a family history

Walsh T, et al. *Proc Natl Acad Sci U S A.* 2011;108(44):18032-18037. Soegaard M, et al. *Clin Cancer Rev.* 2008;14(12):3761-3767. Malander S, et al. *Eur J Cancer.* 2004;40(3):422-428. Risch HA, et al. *J Natl Cancer Inst.* 2006;98(23):1694-1706. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663. Song H, et al. *Hum Mol Genet.* 2014;23(17):4703-4709.

BRCA Testing Among Patients With Ovarian Cancer



6% to 14% of unselected patients with an epithelial ovarian cancer may carry a *BRCA* mutation

Old age at diagnosis or absence of family history does not exclude the presence of a germline mutation

Recent Recommendations for Genetic Testing of Ovarian Cancer

- **Australian National Guidelines (July 2013):**

  Women ≤70 years of age with ovarian cancer can receive genetic testing for *BRCA1/2* mutations, regardless of family history

- **NCCN (V1, February 2014):**

  Epithelial ovarian cancer at any age

- **SGO (March 2014):**

  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

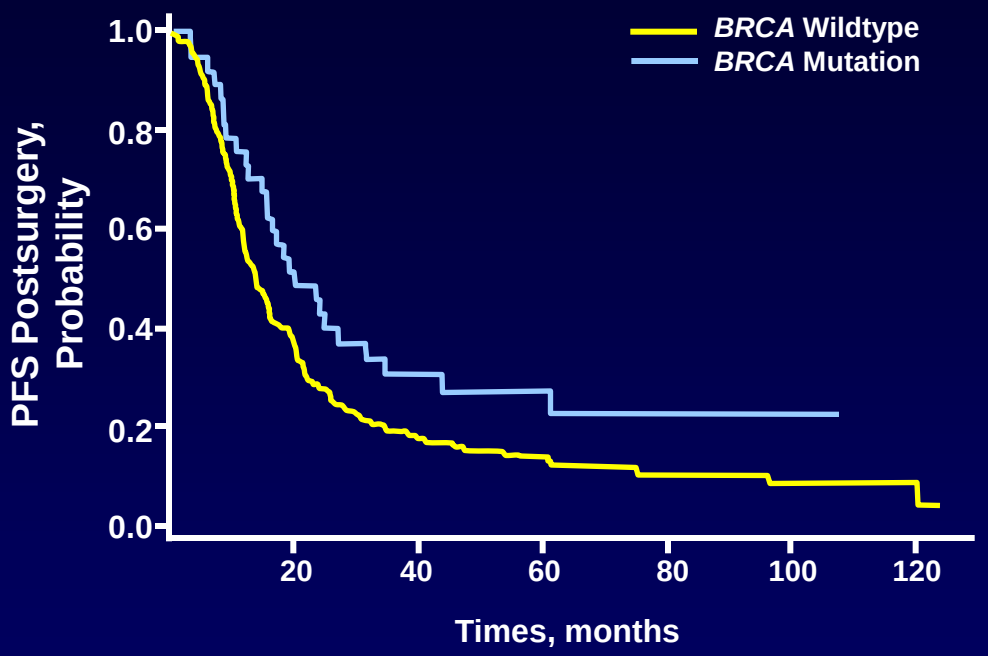
- **Europe: No standardized guidelines, vary by country**

BRCA Somatic Mutations in Ovarian Cancer

	Population	Frequency of Somatic Mutations
Hennessy et al	235 unselected epithelial ovarian cancers	11/235: 5%
TCGA network	489 high-grade serous ovarian cancers	20/316: 6.3%
Alsop et al	1001 nonmucinous ovarian cancers	8/132: 6%
Pennington et al	390 ovarian carcinomas	25/367: 7%
Ledermann et al	265 high-grade, recurrent ovarian carcinomas, platinum-sensitive	18/265: 7%

Hennessy BT, et al. *J Clin Oncol.* 2010;28(22):3570-3576. The Cancer Genome Atlas Research Network. *Nature.* 2011;474(7353):609-615. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663. Pennington P, et al. *Clin Cancer Res.* 2014;20(3):764-775. Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

Somatic Mutations in *BRCA1* and *BRCA2*



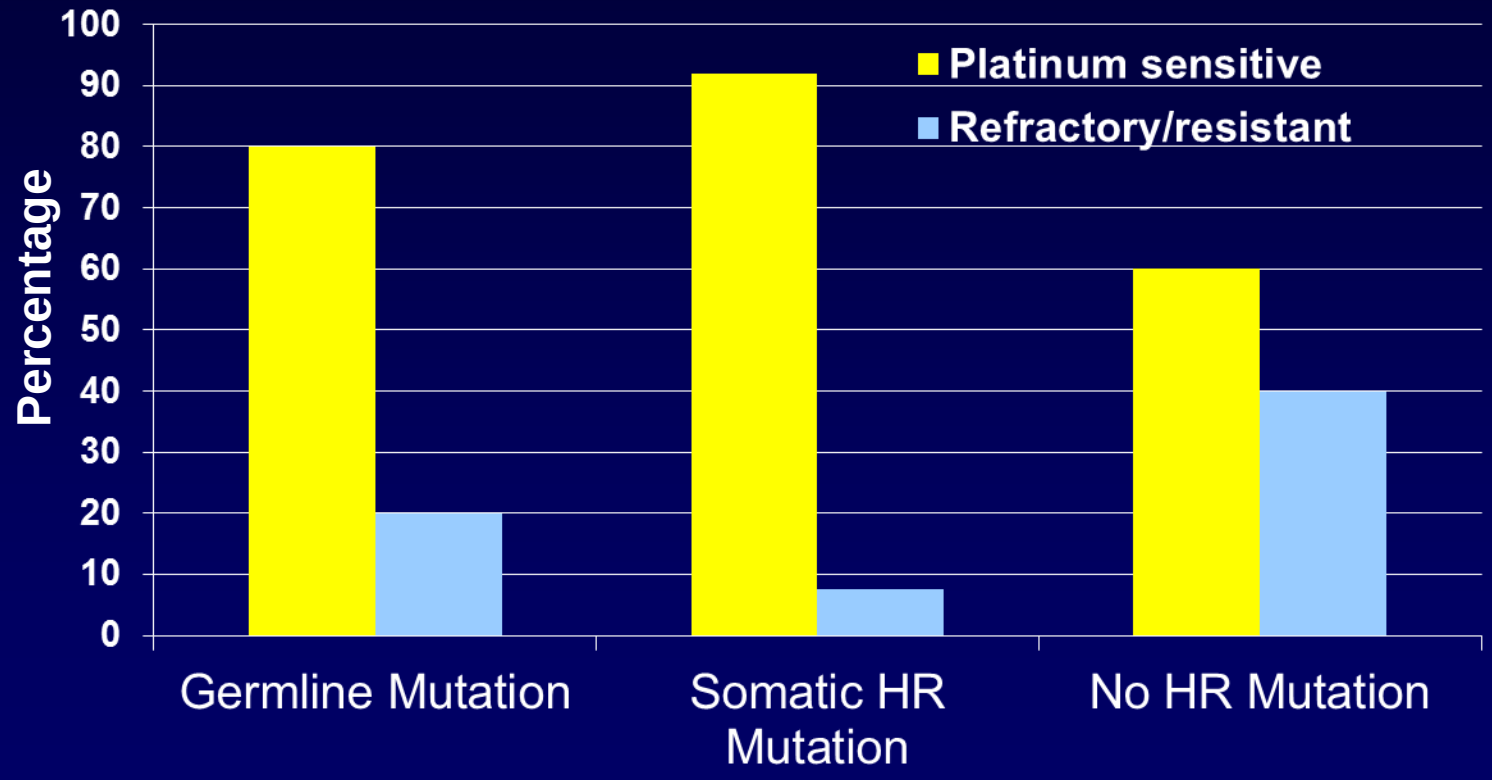
Multivariable Cox Model of PFS in Women With Ovarian Cancer

Variable	*P*	Hazard Ratio	95% CI
Residual disease	.003	1.80	1.25 to 2.59
Stage	.002	2.43	1.30 to 4.54
Grade	.027	1.76	1.03 to 2.99
BRCA1/2 mutation status	.019	0.61	0.39 to 0.94

Hennessy BT, et al. *J Clin Oncol.* 2010;28(22):3570-3576.

- 235 unselected ovarian cancers
- 44 mutations:
  - 30% were somatic
  - Somatic mutations were more frequently novel
- No somatic mutations detected in tumors from patients with germline mutations
- PFS was not significantly different based upon the origin of the mutation (*P* = .69)

Germline and Somatic HR Mutations Predictive of Platinum Sensitivity



Pennington P, et al. *Clin Cancer Res.* 2014;20(3):764-775.

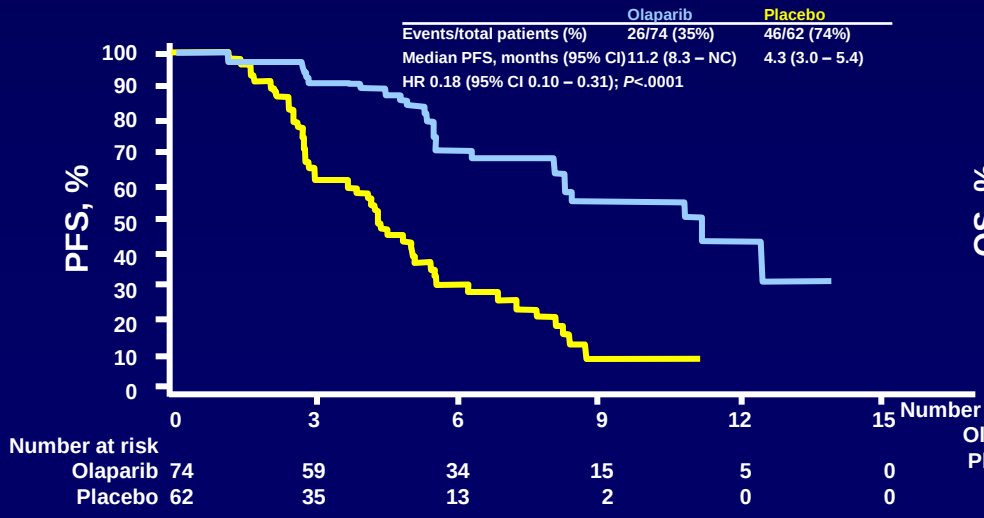
- **25% (4/16) of tumors responding to platinum on a third occasion had a pathogenic somatic *BRCA* mutation (Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663.)**

Olaparib Maintenance Therapy in Patients With Platinum-Sensitive Relapsed Serous Ovarian Cancer: A Preplanned Retrospective Analysis of Outcomes by *BRCA* Status in a Randomized Phase II Trial

- 136/254 (51%) *BRCA1* or *BRCA2* mutated: 96 germline, 18 somatic (7%)
- Small group, but not differences according to mutation origin (ie, germline or somatic)

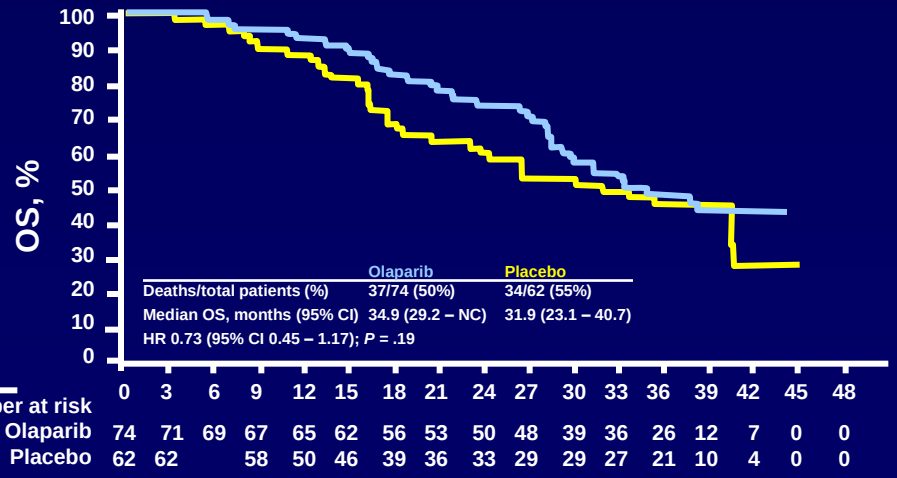
PFS

Patients with *BRCA* mutation (n = 136)



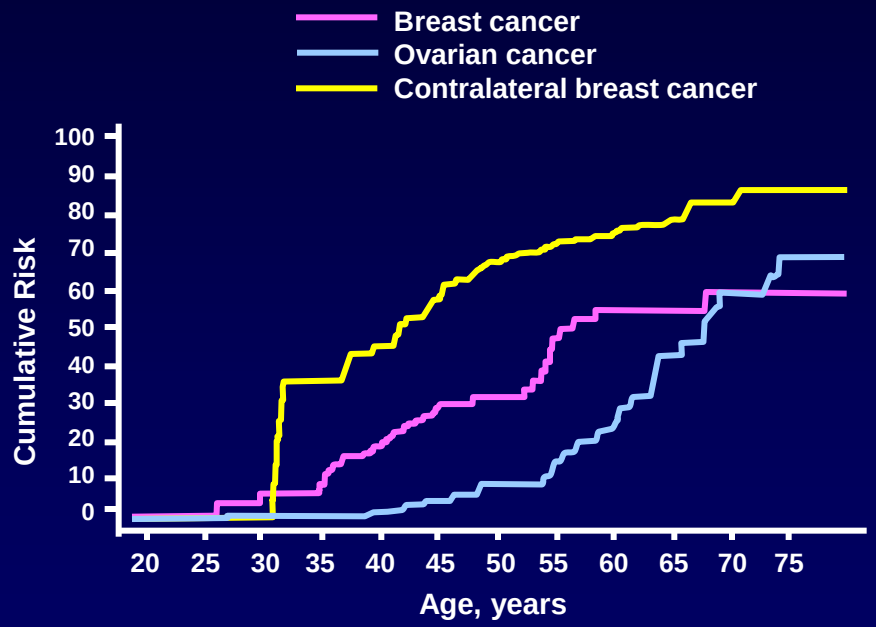
OS

Patients with *BRCA* mutation (n = 136)

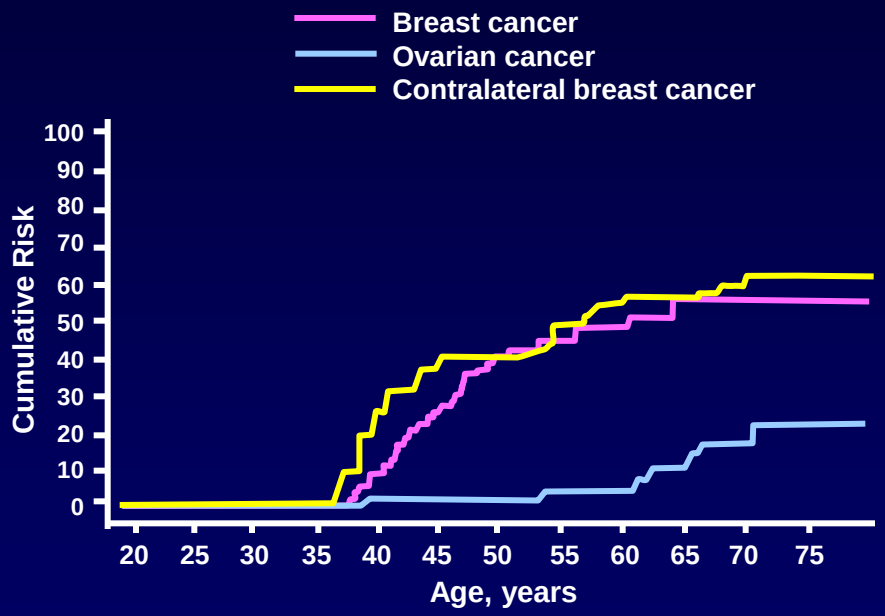


Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

BRCA1



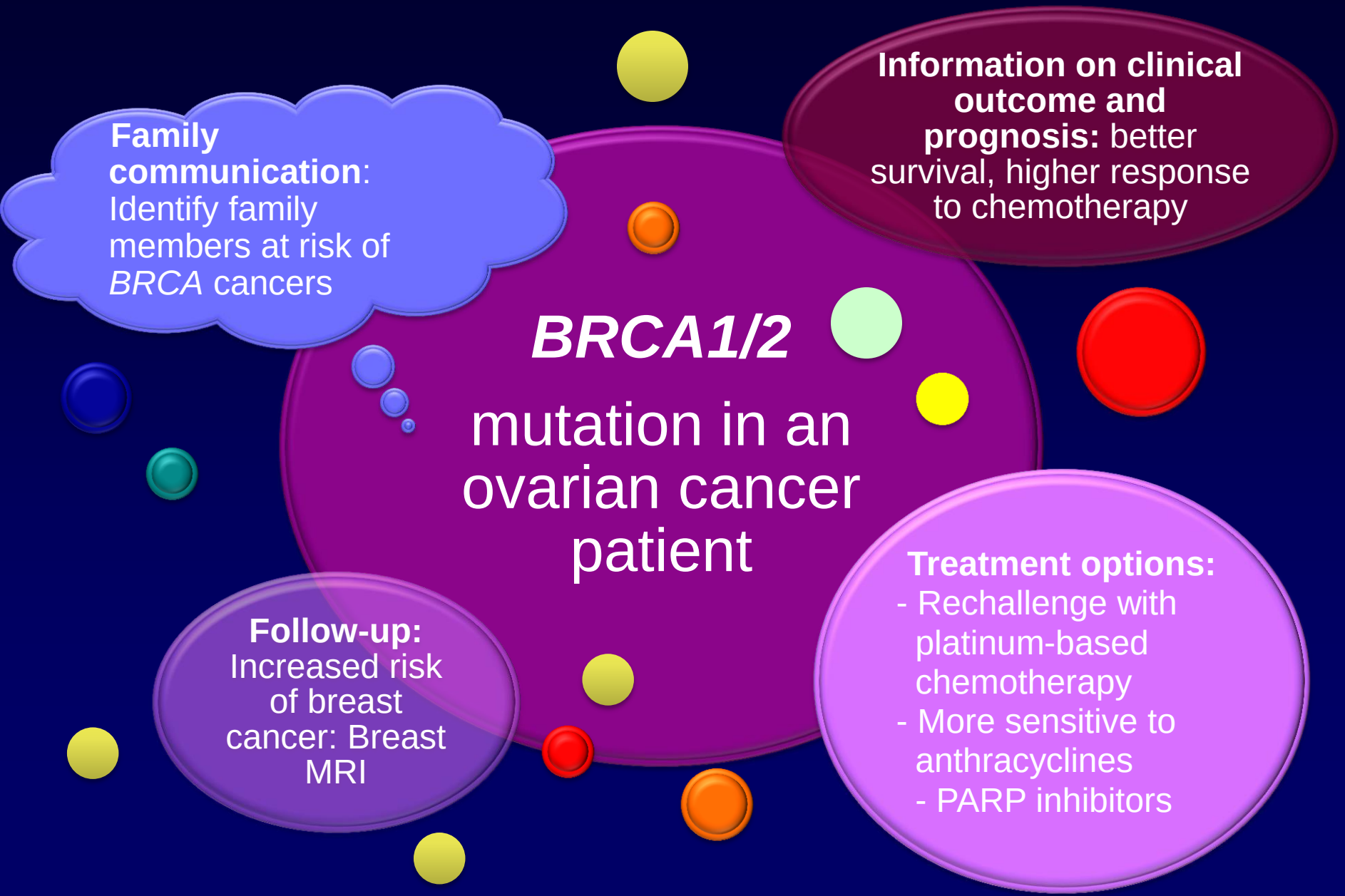
BRCA2



5-year survival ovarian cancer:

BRCA1	44%
BRCA2	61%
No mutation	25%

Yang D, et al. *JAMA.* 2011;306(14):1557-1565. Mavaddat N, et al. *J Natl Cancer Inst.* 2013;105(11):812-822.

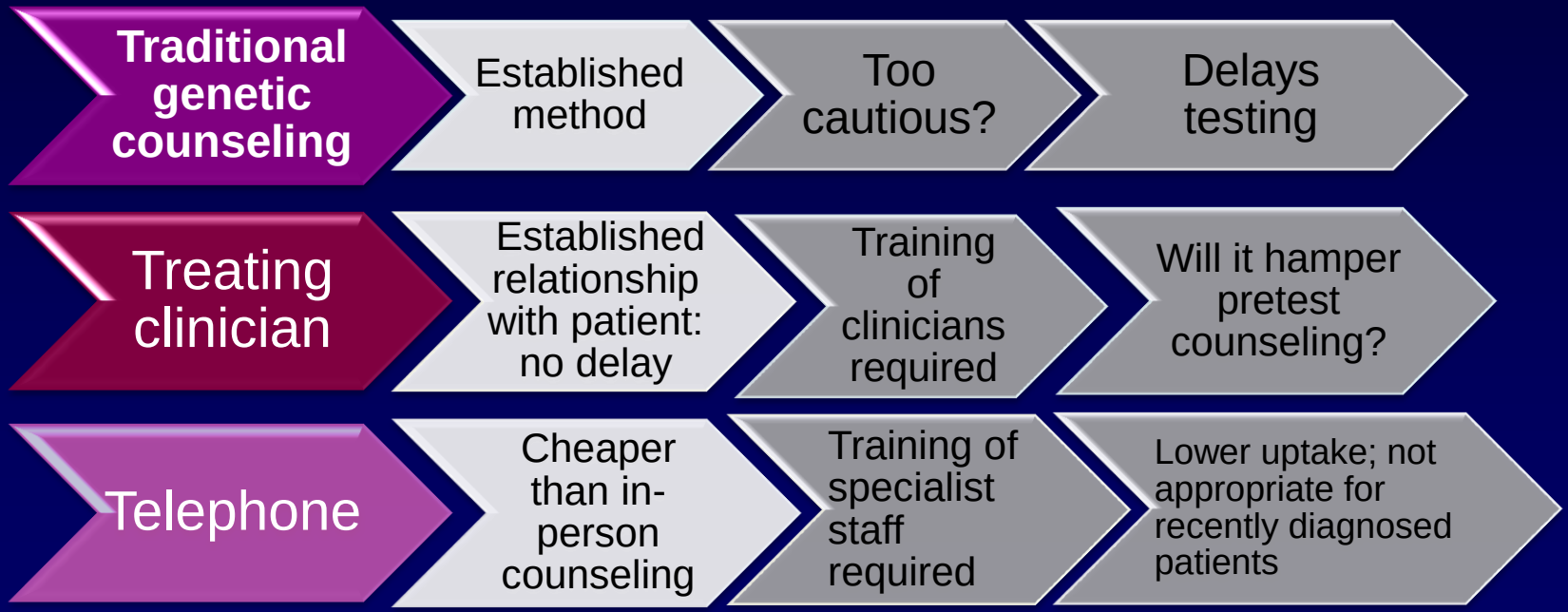

Family communication: Identify family members at risk of *BRCA* cancers
Information on clinical outcome and prognosis: better survival, higher response to chemotherapy
BRCA1/2
mutation in an ovarian cancer patient
Follow-up: Increased risk of breast cancer: Breast MRI
Treatment options:
- Rechallenge with platinum-based chemotherapy
- More sensitive to anthracyclines
- PARP inhibitors

How *BRCA* Testing May Change With the Introduction of Specific *BRCA* Therapies

- More patients referred for testing
- Quicker results needed
- Testing may take place earlier – at diagnosis or during early treatment phase
- Role/timing of counseling may change

Clinical Use of *BRCA* Genetic Testing

Genetic Counseling Models



Meiser B, et al. *Gynecol Oncol.* 2012;124(1):153-157. Schwartz MD, et al. *J Clin Oncol.* 2014;32(7):618-626. Aire S, BMJ 2014; Sie AS, et al. *Fam Cancer.* 2013;12(4):675-682.

Conclusions

- Approximately 10% of invasive epithelial nonmucinous, ovarian cancers are associated with a germline *BRCA1/2* mutations
- Somatic *BRCA* mutations are identified in approximately 5% to 7% of epithelial ovarian cancer
- Around 1/3 of *BRCA* carriers with ovarian cancer do not have a family history of breast/ovarian cancer, or have been diagnosed at an age >60 years

Conclusions

- *BRCA*-carriers with ovarian cancer have better outcomes and are more sensitive to platinum-based chemotherapy and PARPi than noncarriers
- Patients with invasive epithelial ovarian cancer should be considered for *BRCA* testing
- A germline *BRCA* mutation is not a conventional biomarker: multiple clinical and familial implications

Integrating New Therapies Into Ovarian Cancer Management: Does *BRCA* Status Matter?