Testing for *BRCA* Gene Mutations: Why, When, and For Whom?

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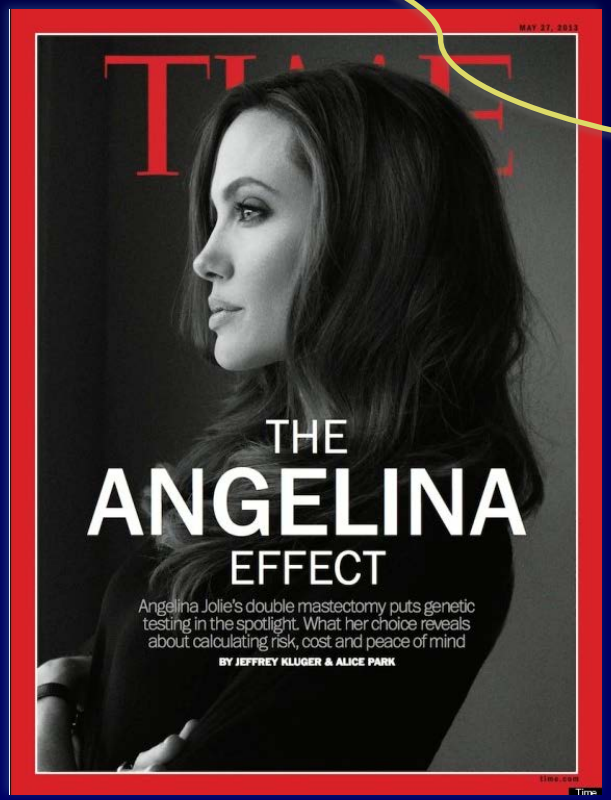
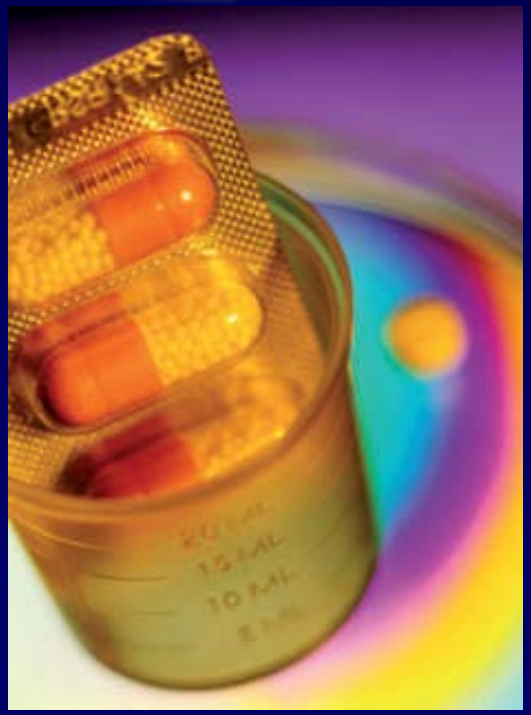
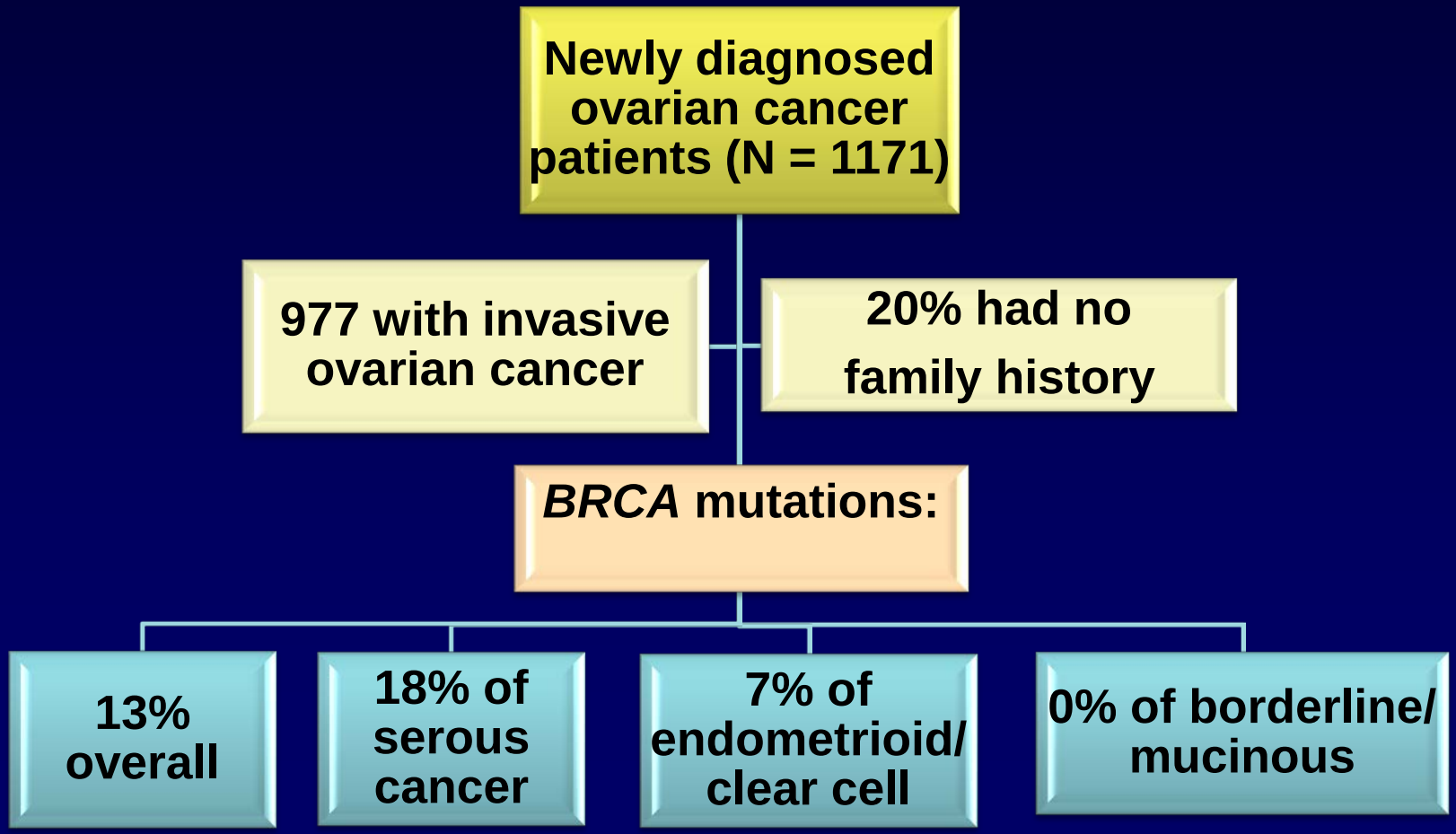
What Are the Reasons to Undergo *BRCA* Genetic Testing?



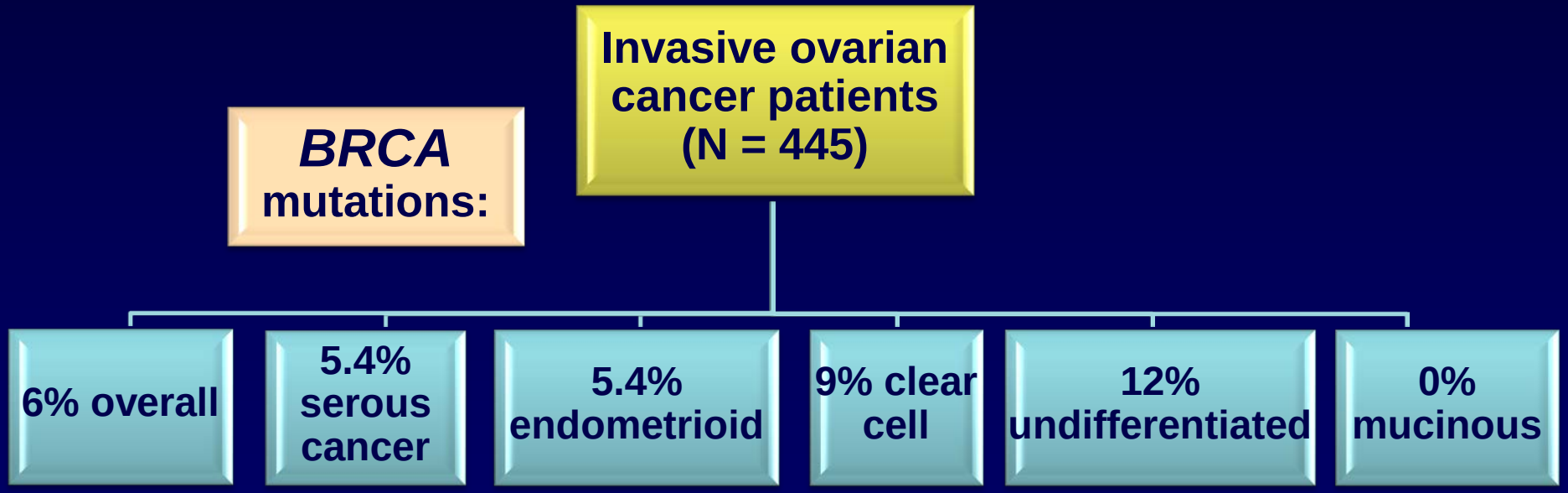


Canadian Study in Unselected Patients With Newly Diagnosed Ovarian Cancer



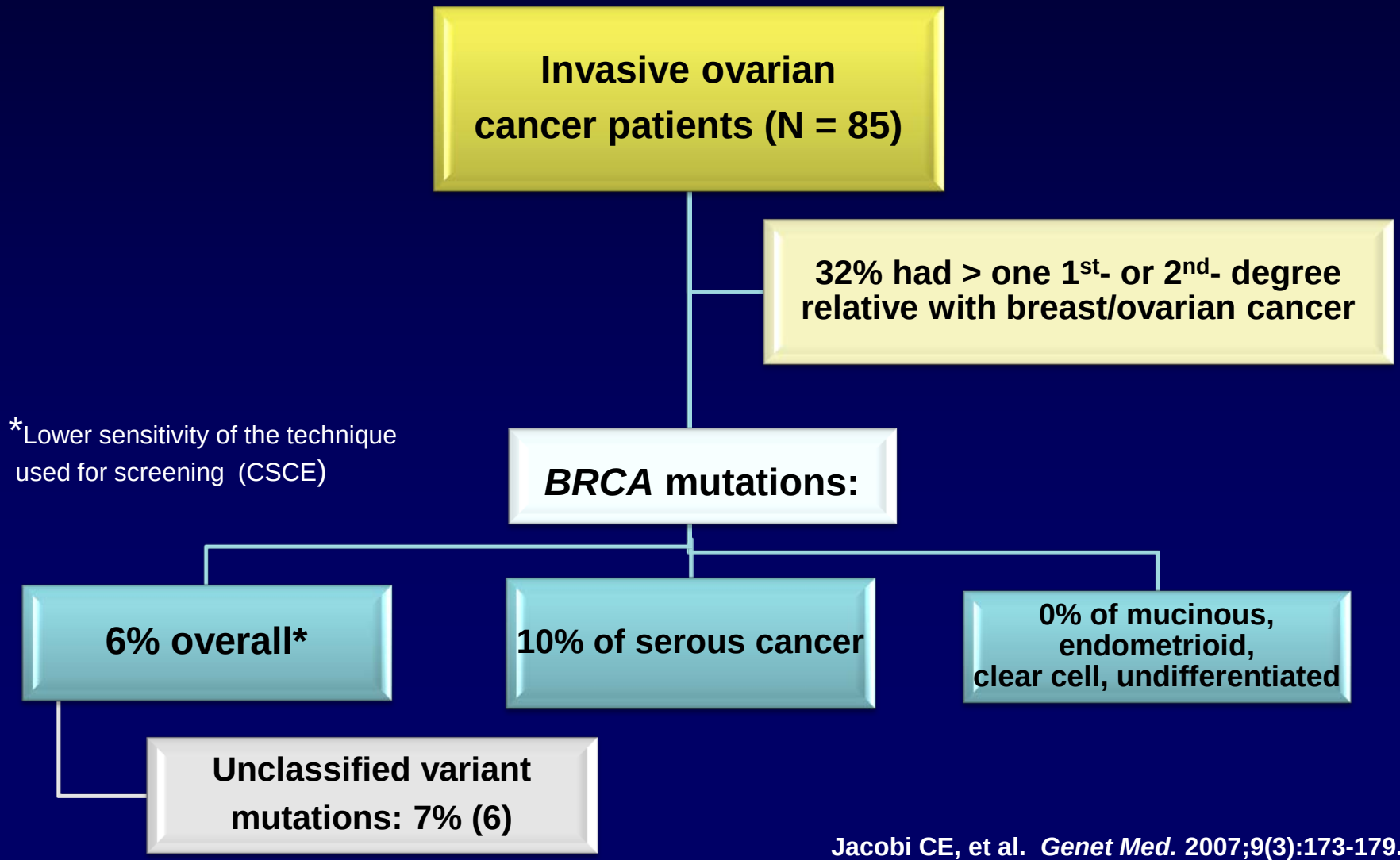
Risch HA, et al. *J Natl Cancer Inst*. 2006;98(23):1694-1706

Danish Study in Population-Based Patients With Ovarian Cancer



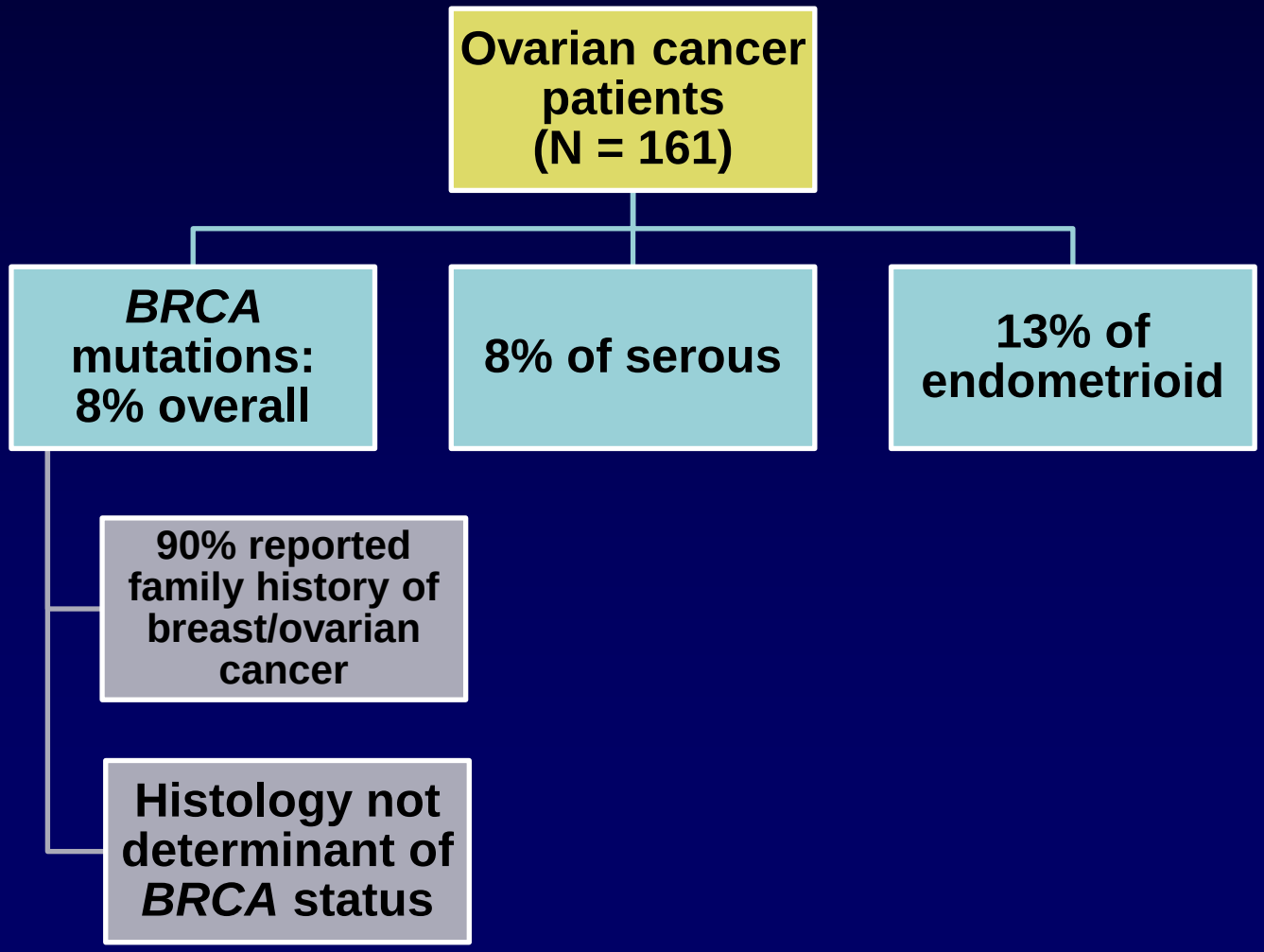
Soegaard M , et al. *Clin Cancer Res.* 2008;14(12):3761-3767.

Dutch Study in Unselected Patients With Primary Diagnosis of Invasive Ovarian Cancer



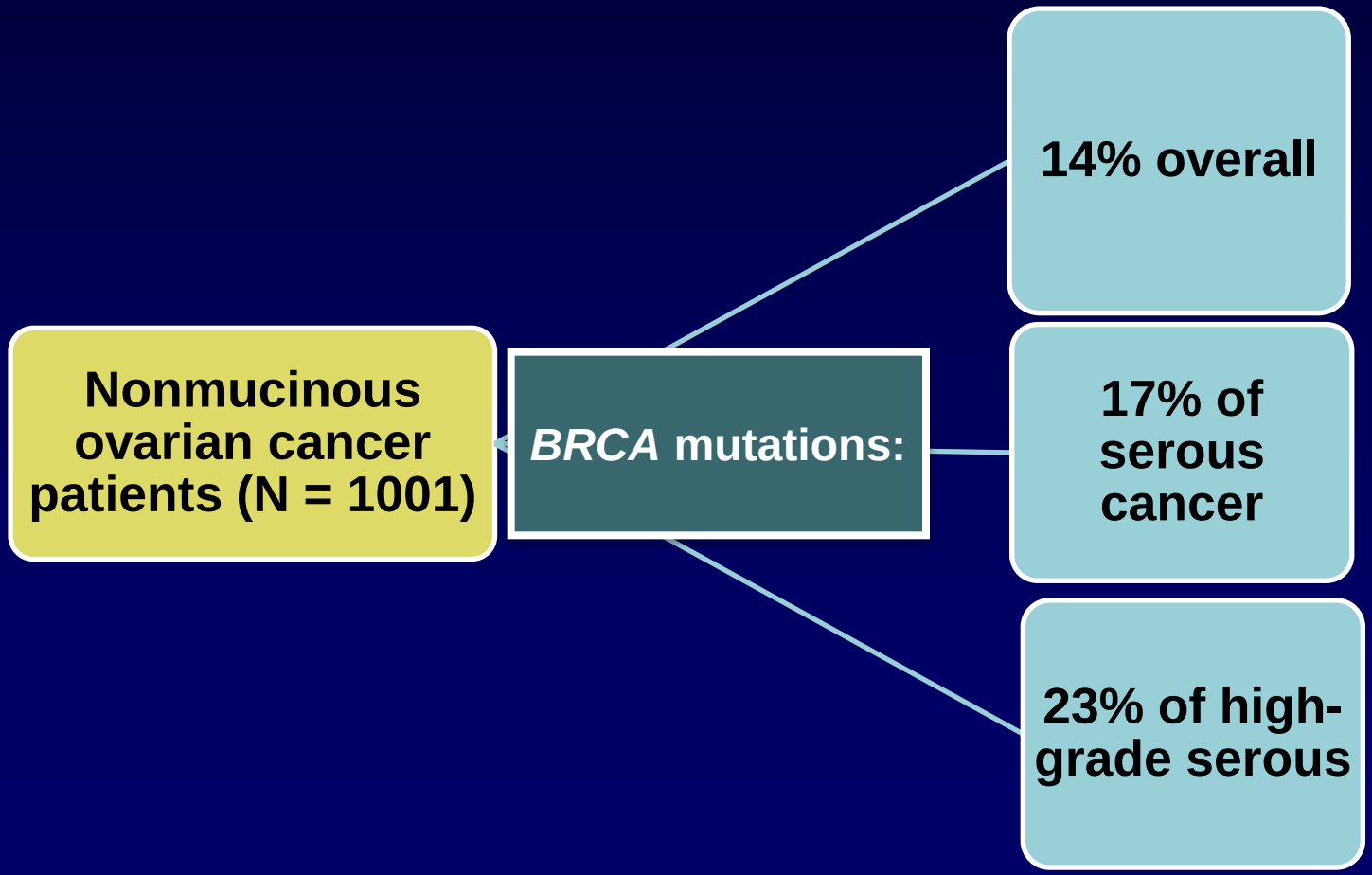
Jacobi CE, et al. *Genet Med.* 2007;9(3):173-179.

Swedish Study in Unselected Patients With Ovarian Cancer



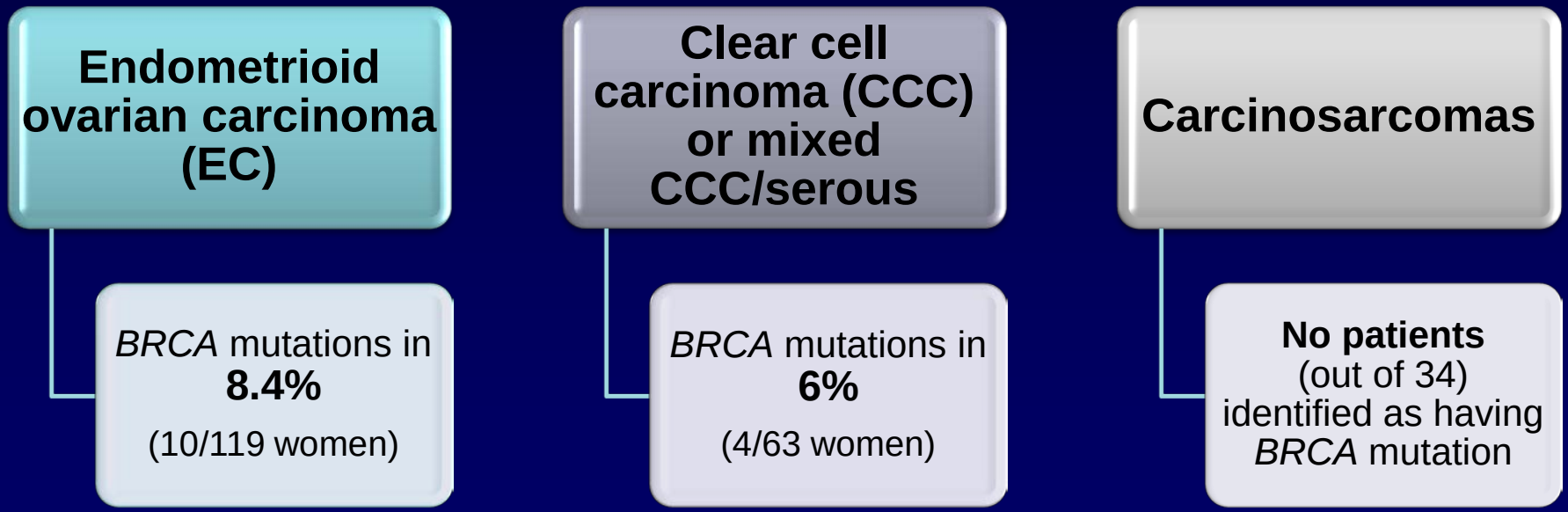
Malander S , et al. *Eur J Cancer.* 2004;40(3):422-428.

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



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

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



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

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

	BRCA1/2 mutation negative	*BRCA1* mutation positive	*BRCA2* mutation positive
Alsop et al	60.5 y	53.4 y	59.8 y
Soegaard et al	61 y	49 y	
Jacobi et al	57.1 y	61.9 y	
Risch et al	55.6 y	51.2 y	57.5 y

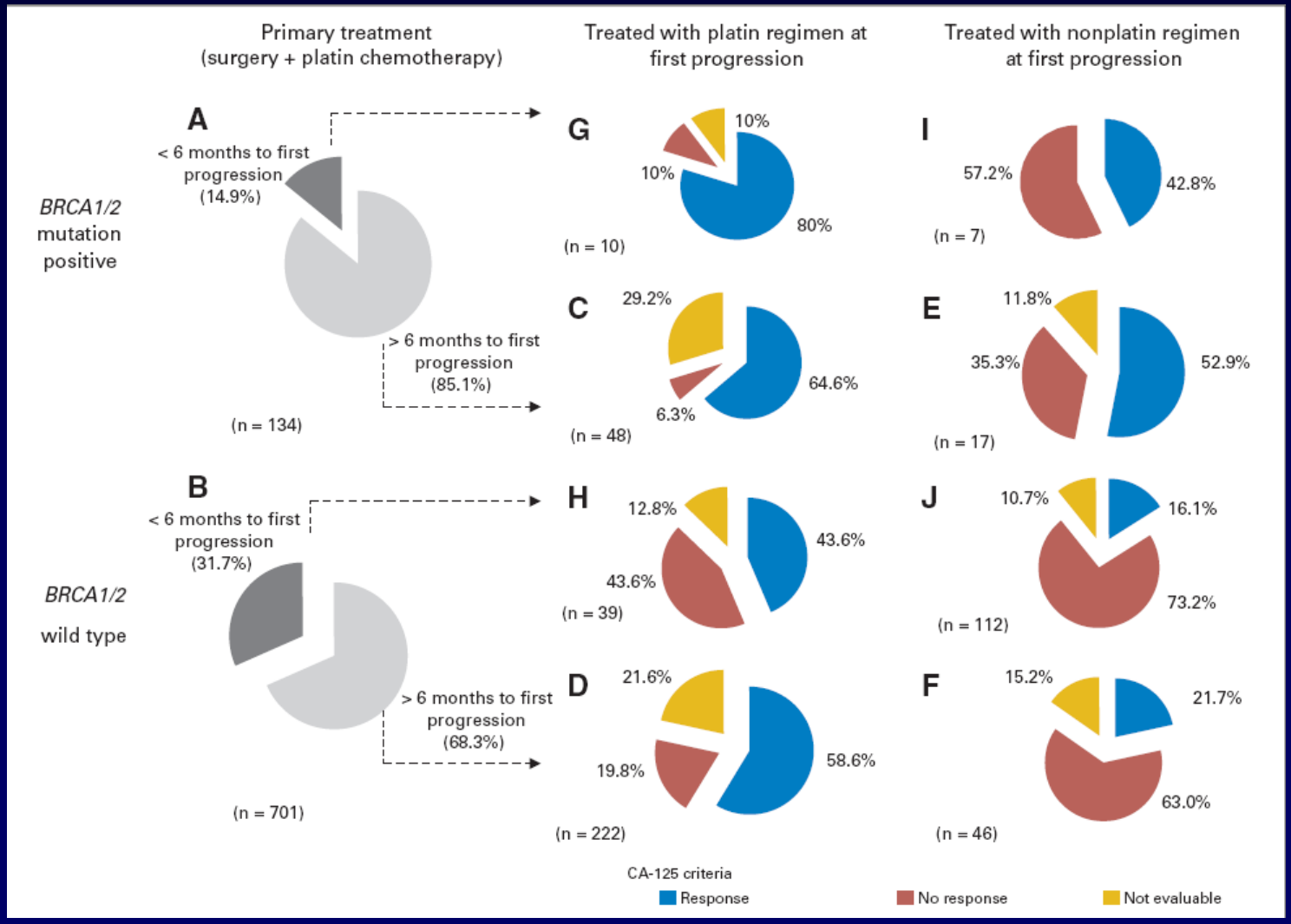
Approximately 25% of *BRCA1/2* mutation carriers are older than 60 years

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

	Absence of family history (breast/ovarian) among *BRCA* mutation carriers
Walsh et al	30%
Alsop et al	44%
Soegaard et al	54%
Malander et al	10%
Jacobi et al	20%
Risch et al	20%

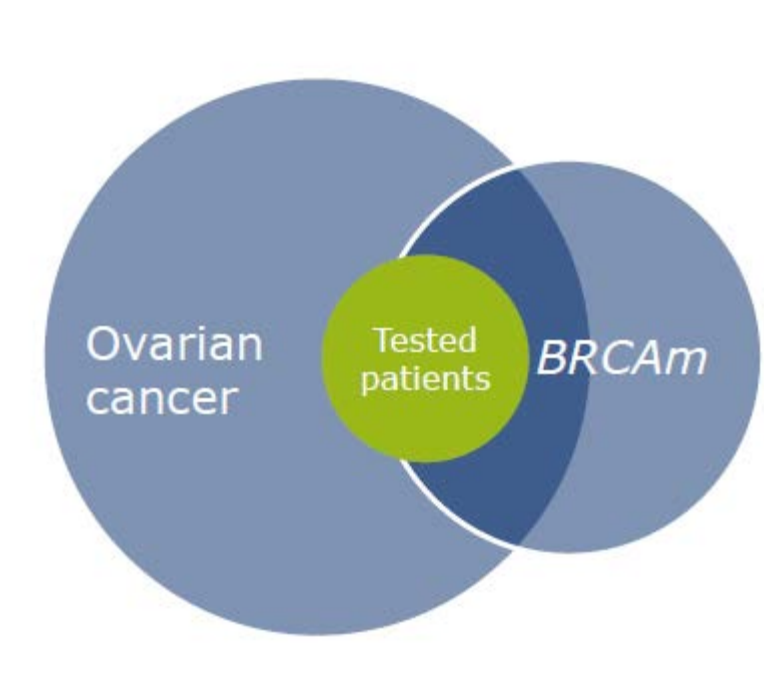
Approximately 30% of *BRCA1/2* mutation carriers do not have a family history

Might Platinum Response Be Predictor of Germline *BRCA* Mutation?



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

BRCA Testing Among Ovarian Cancer Patients



6%-14% of unselected patients with an epithelial OvC 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 *BRCA 1/2* 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

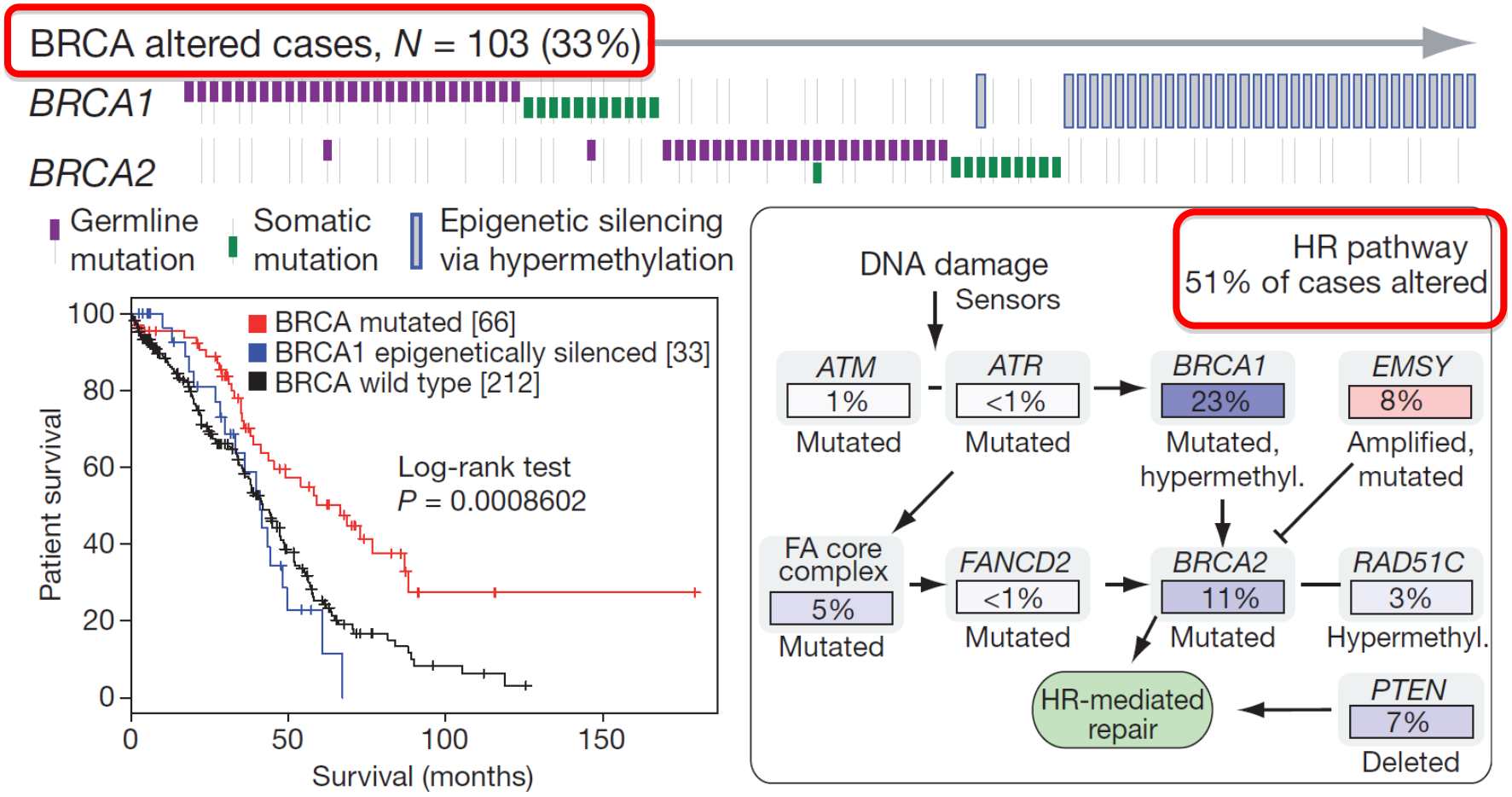
- **ESMO (2013):**

  There are no clear guidelines for referral of ovarian cancer patients for testing. Referral is made on the basis of a family history and ethnic background. The importance of identifying BRCA mutations has increased as, in addition to risk-reducing surgery and surveillance for breast cancer in the patient and in family members, there are new treatments emerging specifically for BRCA-related cancers.

Extensive Defects in Homologous Recombination With Mutual Exclusivity (TCGA Data)

BRCA mutations:
17% germline
3% somatic

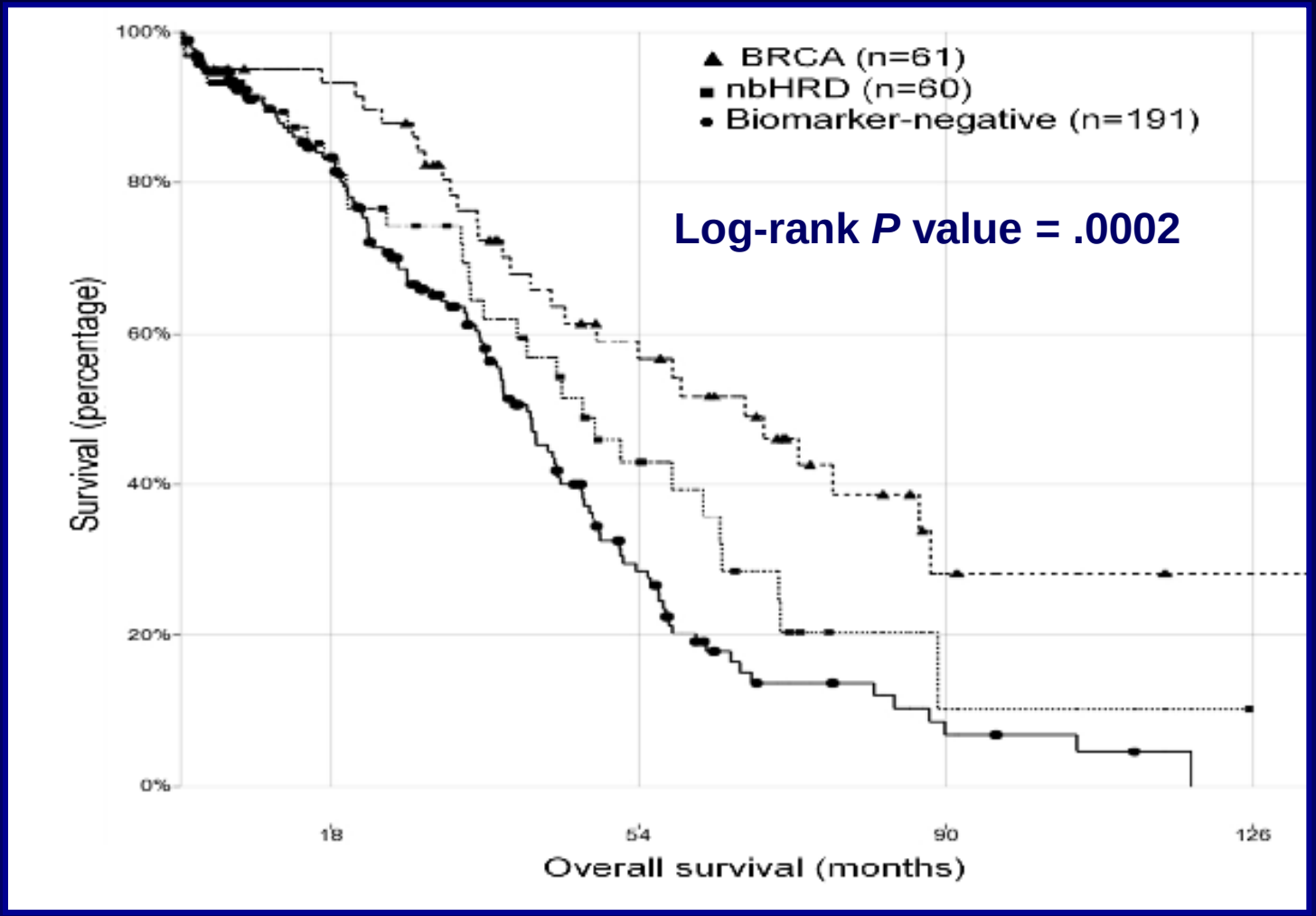
Homologous Repair (HR) Alterations



TCGA, The Cancer Genome Atlas

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

Patients With *BRCA* or *nbHRD* Mutations Treated With Platinum-Based Therapies Experience Longer Overall Survival



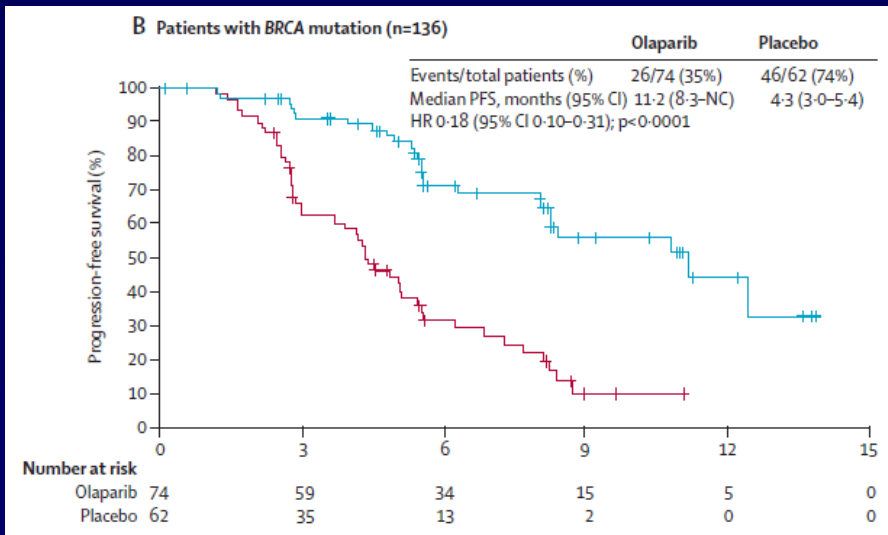
Kaplan-Meier analysis of the publicly available TCGA ovarian cancer dataset

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

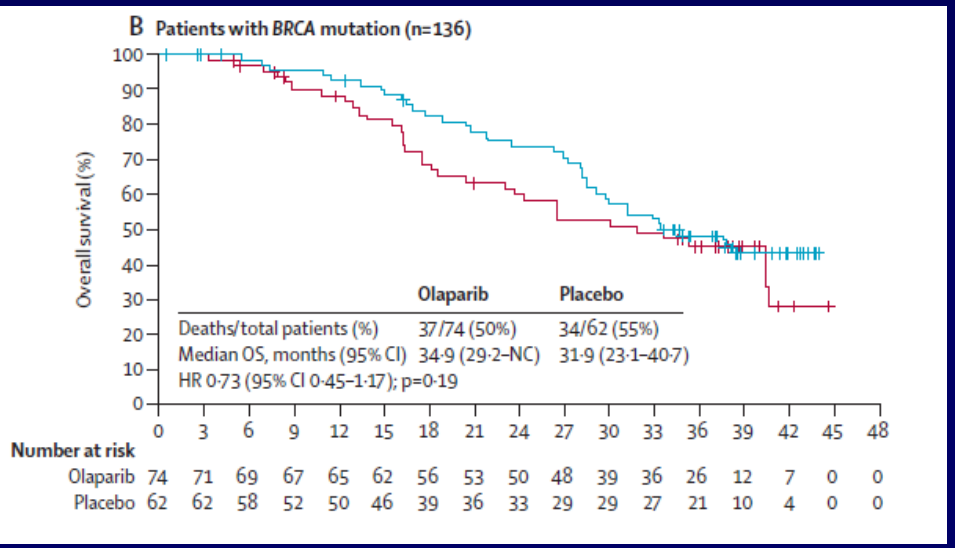
Lancet Oncol 2014; 15: 852–61

- **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)**

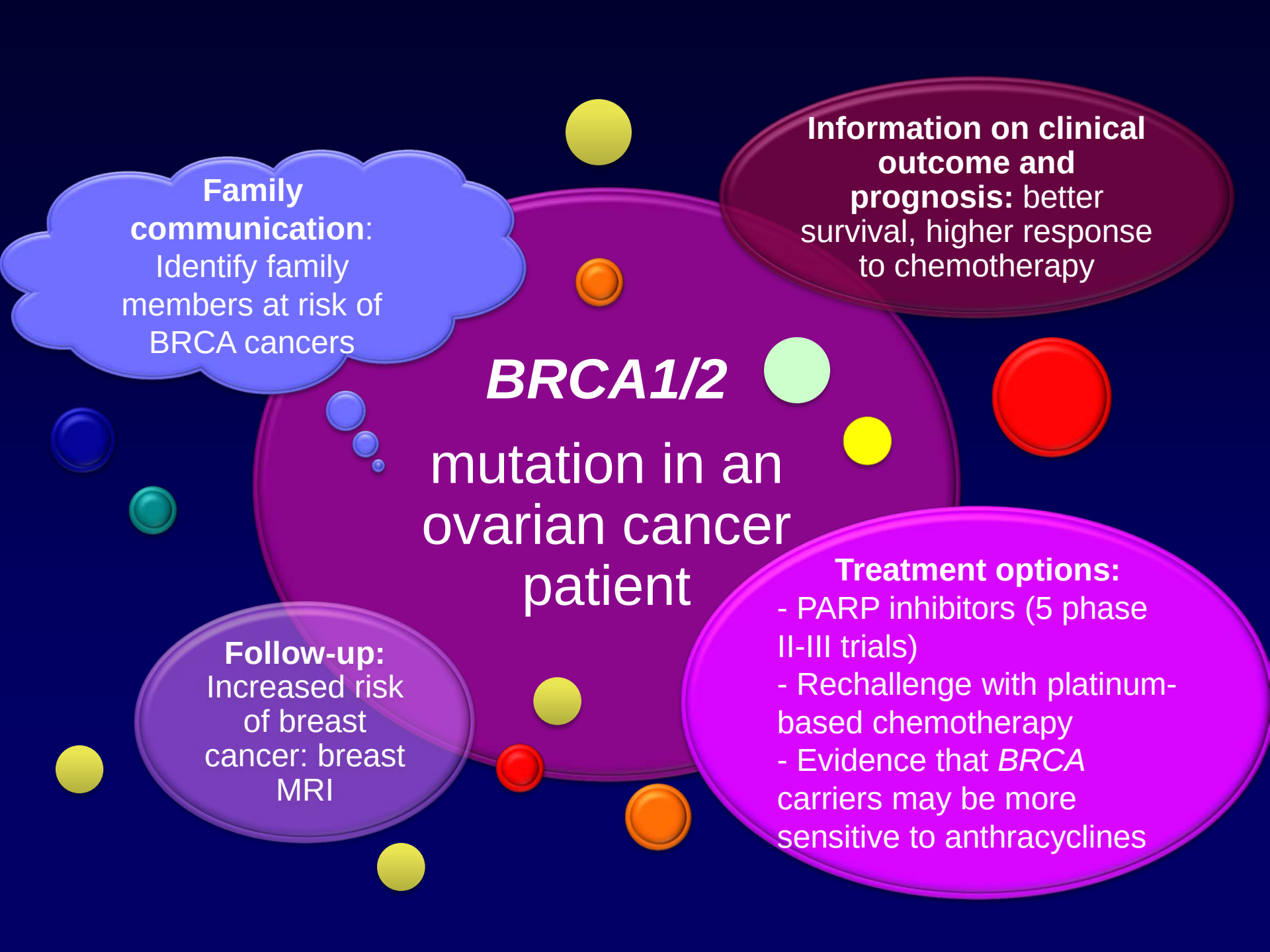
PFS



OS



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

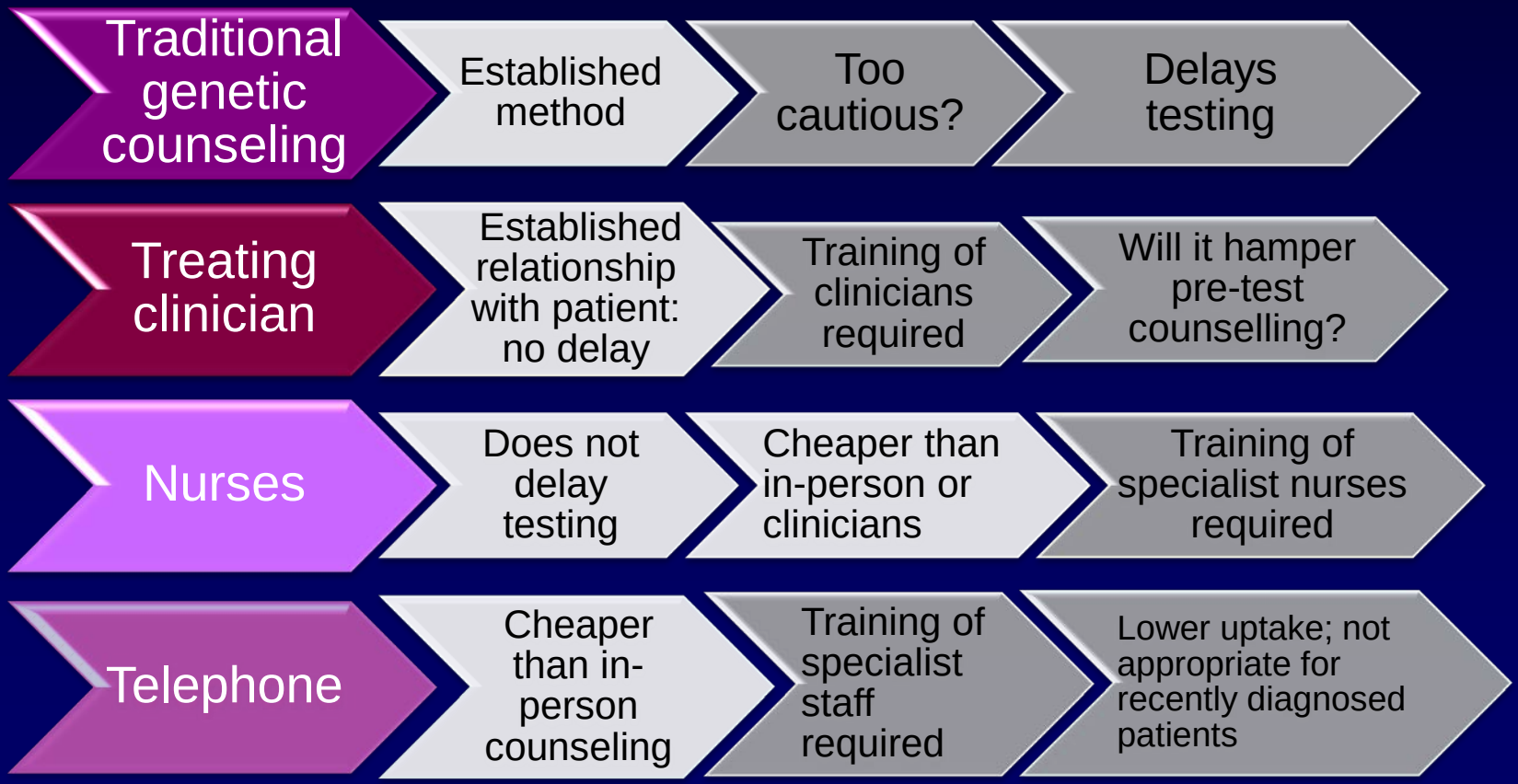

Family communication: Identify family members at risk of BRCA cancers
Information on clinical outcome and prognosis: better survival, higher response to chemotherapy
BRCA1/2
mutation in an ovarian cancer patient
Follow-up: Increased risk of breast cancer: breast MRI
Treatment options:
- PARP inhibitors (5 phase II-III trials)
- Rechallenge with platinum-based chemotherapy
- Evidence that BRCA carriers may be more sensitive to anthracyclines

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

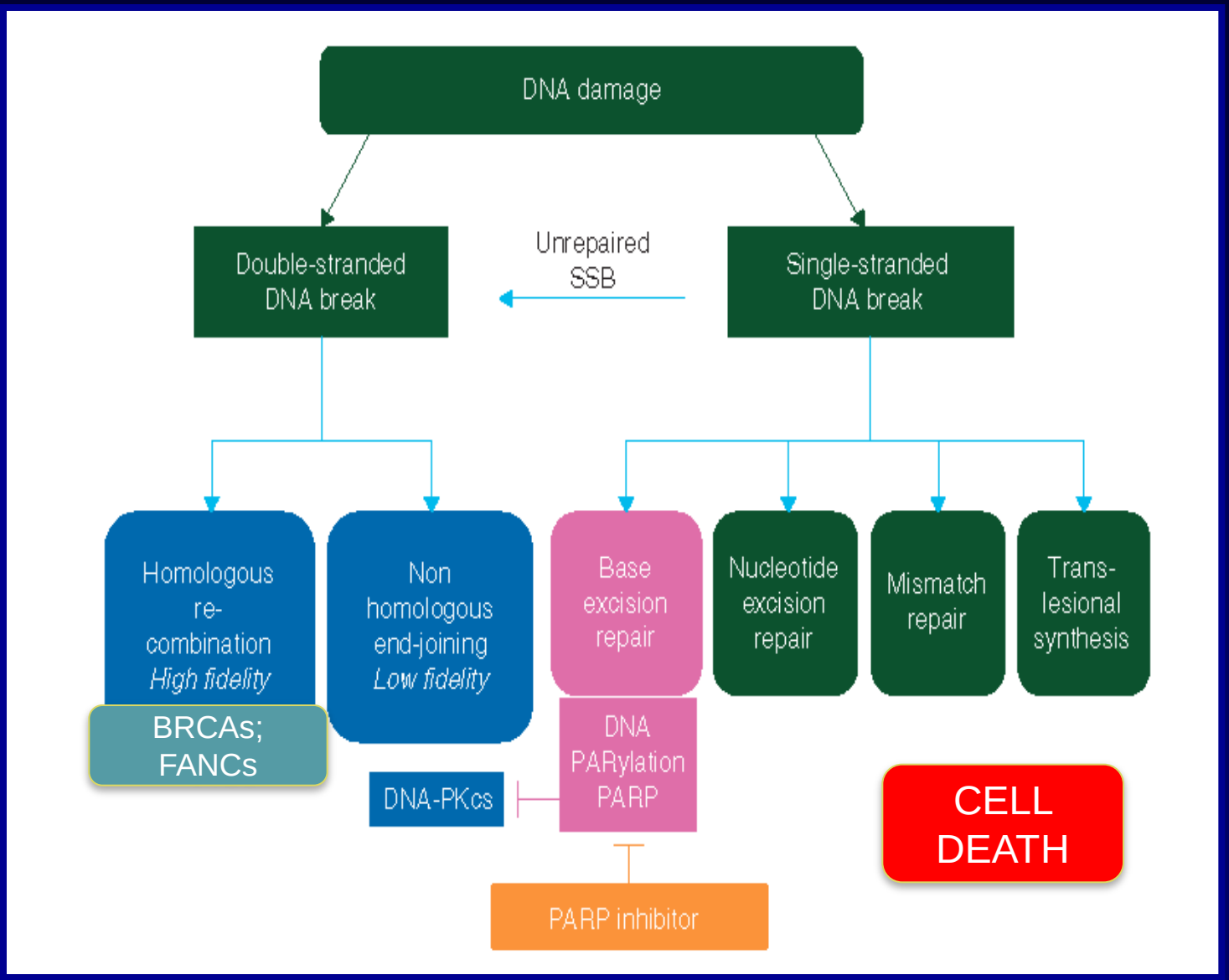
Clinical Use of *BRCA* Genetic Testing

Genetic Counseling Models

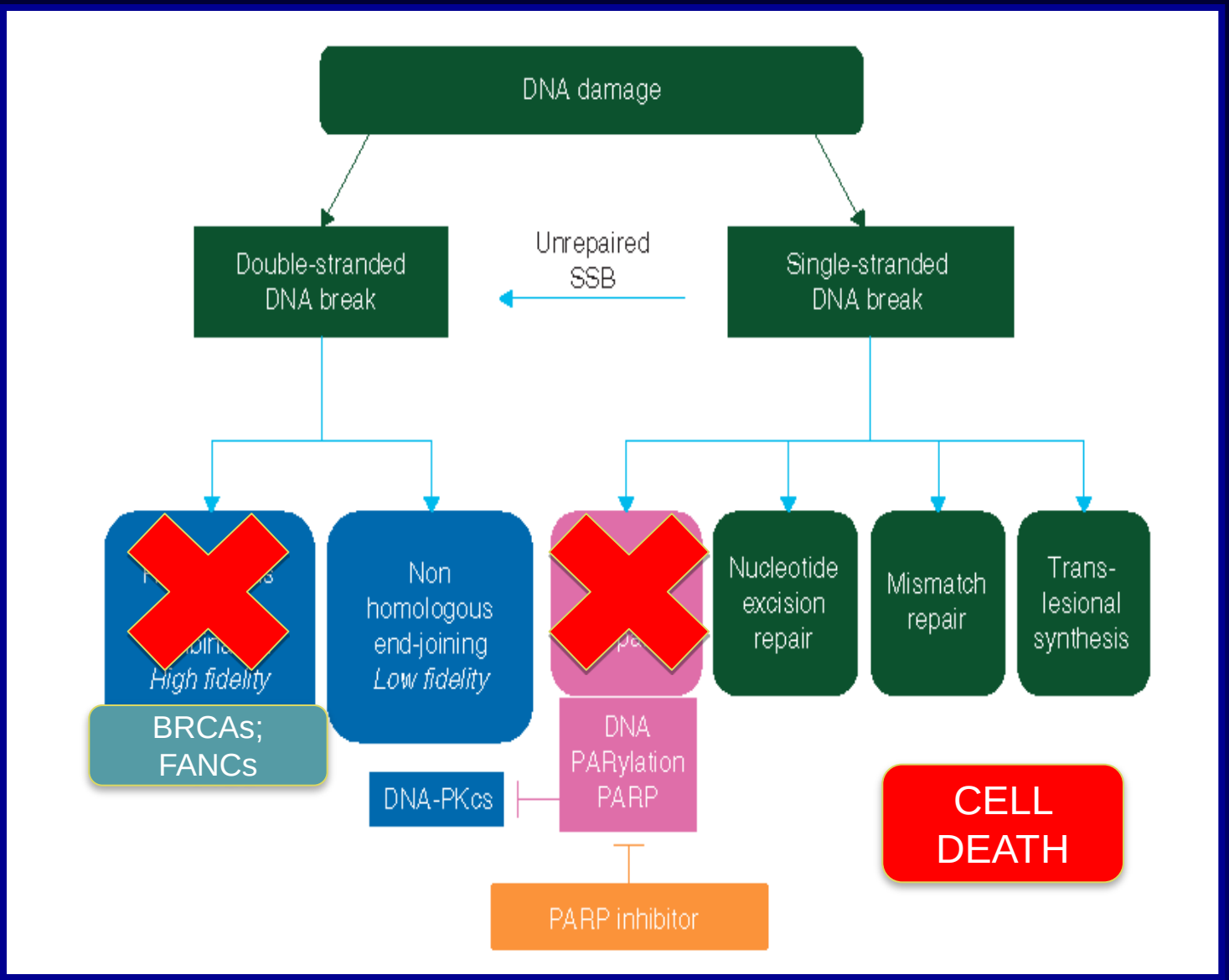


Meiser B, et al. *Gynecol Oncol.* 2012;124(1):153-157; Schwartz MD, et al. *J Clin Oncol.* 2014;32(7):618-626; Sie AS, et al. *Fam Cancer.* 2013;12(4):675-682. George A, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 881PD.

DNA Damage Repair Pathways



DNA Damage Repair Pathways



Cytotoxic Mechanism of PARP Inhibition

DNA Damage

Homologous Recombination

- *BRCA*1/2
- *Rad*51
- *FA* proteins
- *XRCC3*
- Others (PTEN)

Error-free Repair → Cell Survival

PARP1

NHEJ

- DNA-PK

Error-prone Repair →

- Genomic Instability
- Chromosome rearrangement

→ Cell Death

Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-3411.

Cytotoxic Mechanism of PARP Inhibition

DNA Damage

Homologous Recombination

- *BRCA1*
- *BRCA2*
- *FA proteins*
- *ATM*
- *Others (PTEN)*

Error-free Repair → Cell Survival

PARP1

NHEJ

- DNA-PK

Error-prone Repair → Genomic Instability, Chromosome rearrangement → Cell Death

Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-3411.

Cytotoxic Mechanism of PARP Inhibition

DNA Damage

Homologous Recombination

- *BRCA1*
- *BRCA2*
- *FA proteins*
- *ATM*
- *Others (PTEN)*

Error-free Repair → Cell Survival

PARPi

PARP1

NHEJ

- DNA-PK

Error-prone Repair →

- Genomic Instability
- Chromosome rearrangement

→ Cell Death

Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-3411.

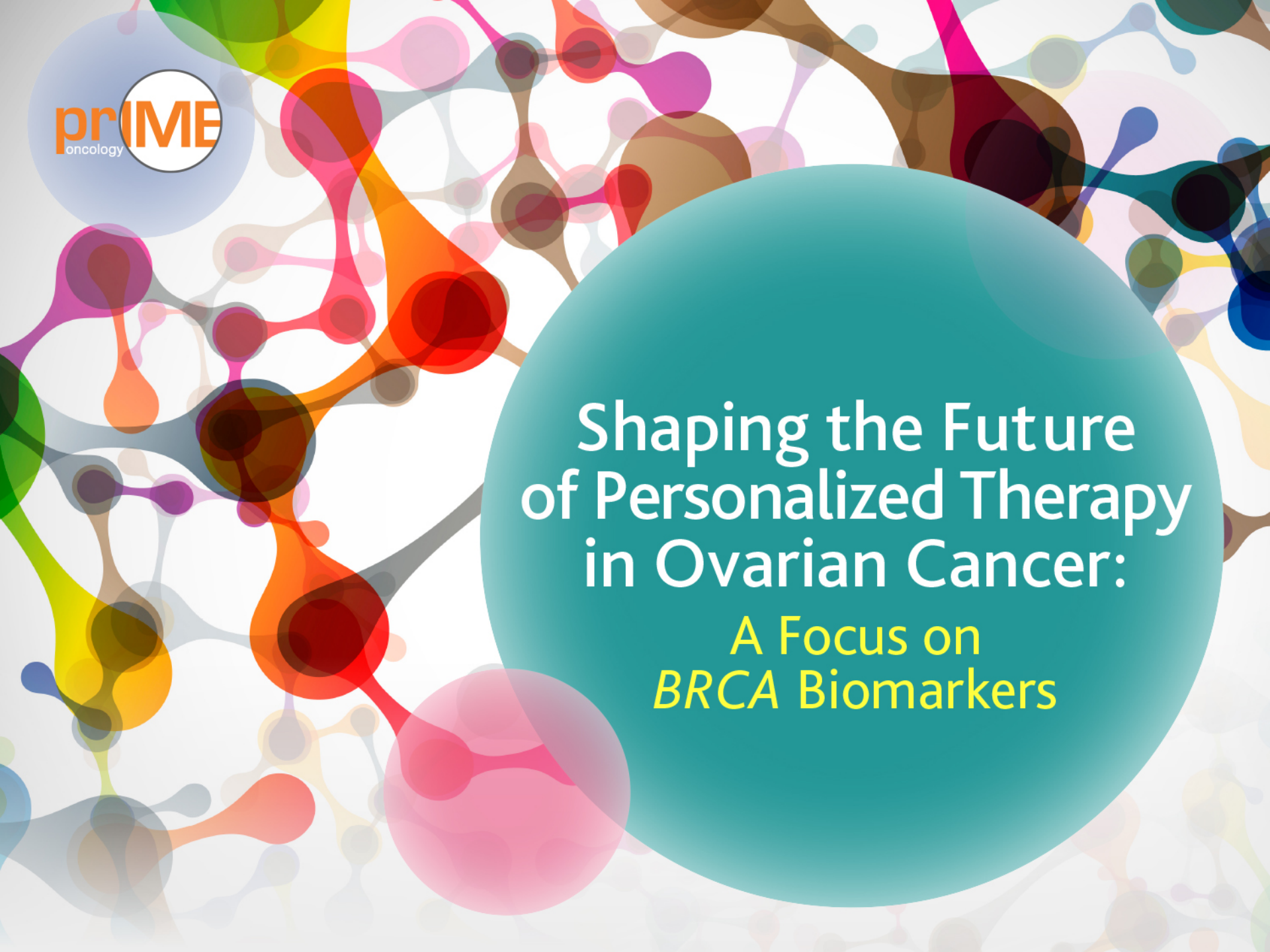
prIME POINTS™

- Approximately 10% of epithelial non-mucinous, non-borderline ovarian cancers are associated with a germline *BRCA1/2* mutations
- Somatic *BRCA* mutations are identified in approximately 3%-7% of high-grade serous 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 >60y

prIME POINTS™

- *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 tested for BRCA at an early stage
- *BRCA* is not a conventional biomarker: multiple implications

A *BRCA* germline mutation is something that an individual carries for the duration of his or her lifetime


prIME
oncology
Shaping the Future of Personalized Therapy in Ovarian Cancer:
A Focus on
BRCA Biomarkers