

Know Your Enemy: The Impact of *BRCA* Status on Management of Ovarian Cancer

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Disclosures

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Collaborations

Clovis Oncology

All honoraria donated



Twenty Years of Chasing *BRCA1/2*:

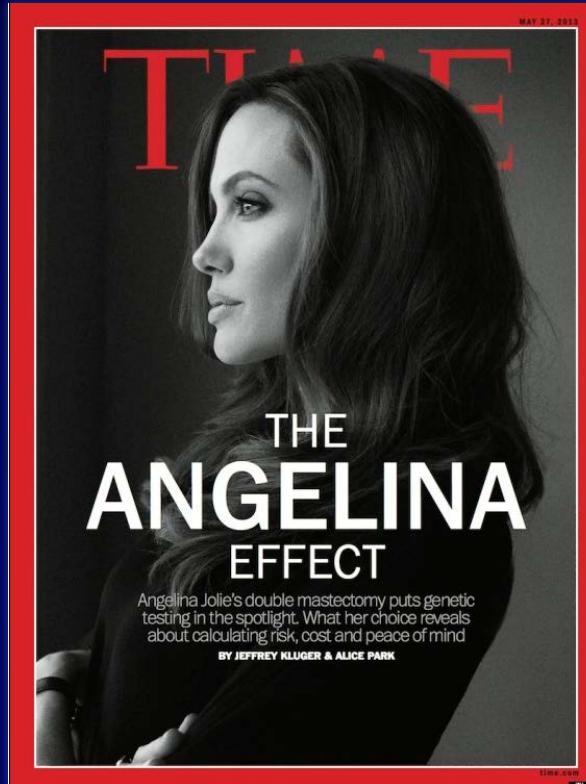
The Impact of Testing

RESEARCH ARTICLES

A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*

Yoshio Miki, Jeff Swensen, Donna Shattuck-Eidens, P. Andrew Futreal, Keith Harshman, Sean Tavtigian, Qingyun Liu, Charles Cochran, L. Michelle Bennett, Wei Ding, Russell Bell, Judith Rosenthal, Charles Hussey, Thanh Tran, Melody McClure, Cheryl Frye, Tom Hattier, Robert Phelps, Astrid Haugen-Strano, Harold Katcher, Kazuko Yakumo, Zahra Gholami, Daniel Shaffer, Steven Stone, Steven Bayer, Christian Wray, Robert Bogden, Priya Dayananth, John Ward, Patricia Tonin, Steven Narod, Pam K. Bristow, Frank H. Norris, Leah Helvering, Paul Morrison, Paul Rosteck, Mei Lai, J. Carl Barrett, Cathryn Lewis, Susan Neuhausen, Lisa Cannon-Albright, David Goldgar, Roger Wiseman, Alexander Kamb, Mark H. Skolnick*

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NATURE • VOL 378 • 21/28 DECEMBER 1995

LETTERS TO NATURE

Identification of the breast cancer susceptibility gene *BRCA2*

Richard Wooster*, Graham Bignell*, Jonathan Lancaster†, Sally Swift†, Sheila Seal*, Jonathan Mangion*, Nadine Collins*, Simon Gregory§, Curtis Gumbs||, Gos Micklem§, Rita Barfoot*, Rifat Hamoudi*, Sandeep Patel*, Catherine Rice§, Patrick Biggs*, Yasmin Hashim*, Amanda Smith†, Frances Connor†, Adalgeir Arason†, Julius Gudmundsson†, David Flicenec***, David Kelsell#, Deborah Ford*, Patricia Tonin**, D. Timothy Bishop††, Nigel K. Spurr*, Bruce A. J. Ponder††, Rosalind Eales*, Julian Peto*, Peter Devilleo§§, Cees Cornelisse§§, Henry Lynch||, Steven Narod***, Gilbert Lenoir††, Valgardur Egilsson*, Rosa Bjork Barkadottir†, Douglas F. Easton##, David R. Bentley§, P. Andrew Futreal†, Alan Ashworth† & Michael R. Stratton*

Incidence and Prevalence

The frequency at which *BRCA1/2* mutations are found
The prevalence of *BRCA1/2* mutations in our population

Prevalence dependent on context:

In the general population: 1:800 – 1:1000

In BC/OC cases unselected for family history (FHx) or age:
1%-7%

?Unselected ovarian cancer cases: higher (13%-14%)

?High-grade serous cancer, <55 yo, FHx BC/OC, or past medical history (PHx) BC

BRCA1/2 Mutations: Hereditary (Germline) or Somatic

Germline: **germline DNA** tested for mutations
vs

Somatic: **tumor DNA** tested for mutations

Nonselected cases of ovarian cancer:
high-grade epithelial ovarian cancer (nonmucinous)

High-grade serous cancer, <55yo, FHx BC/OC or PHx BC

BRCA1/2 Germline Mutations: Risk of Ovarian Cancer

Cases unselected for family history
average cumulative risks by age 70 years:

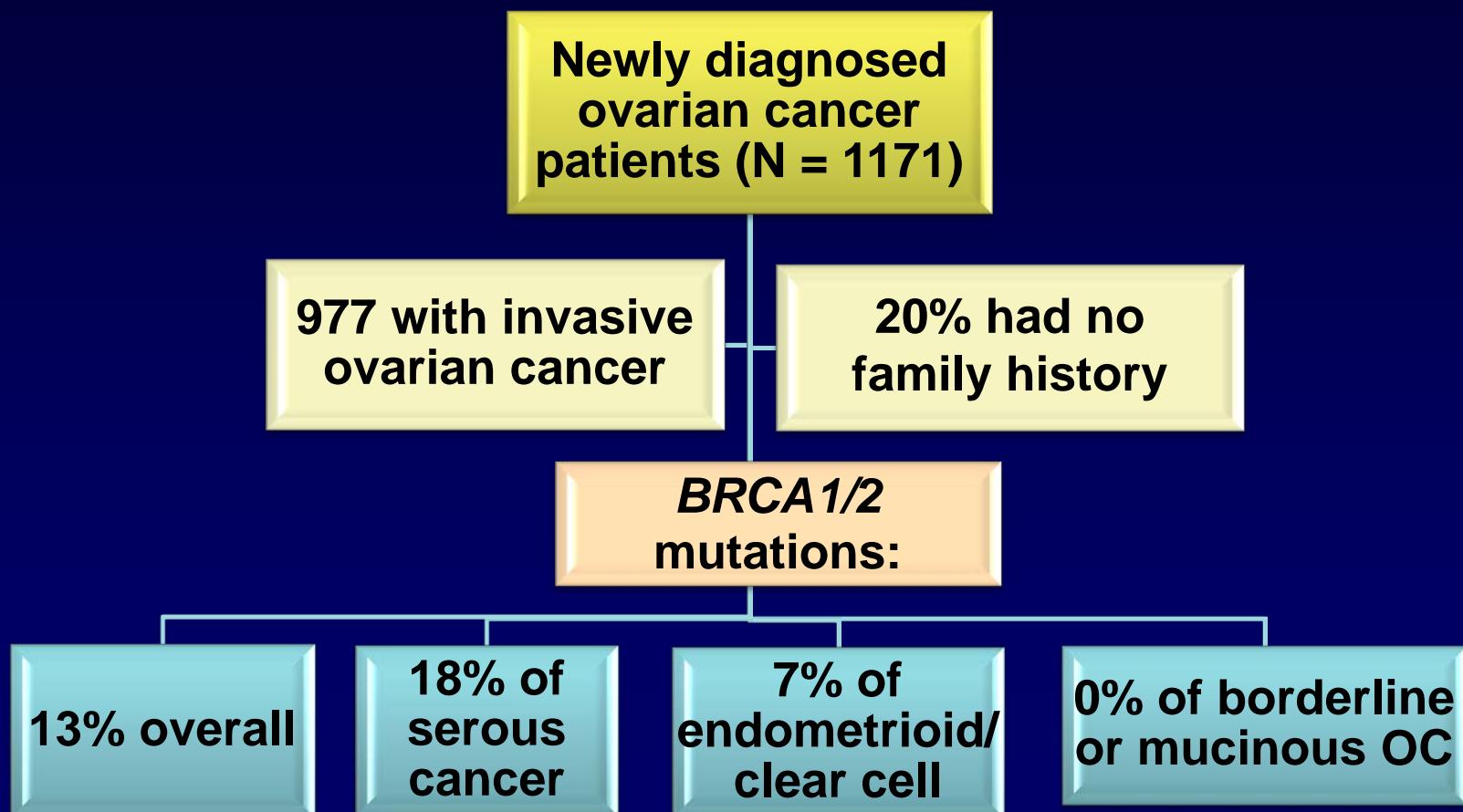
BRCA1 mutation carriers:

Breast cancer: 65% (44%–78%)
Ovarian cancer: 39% (18%–54%)

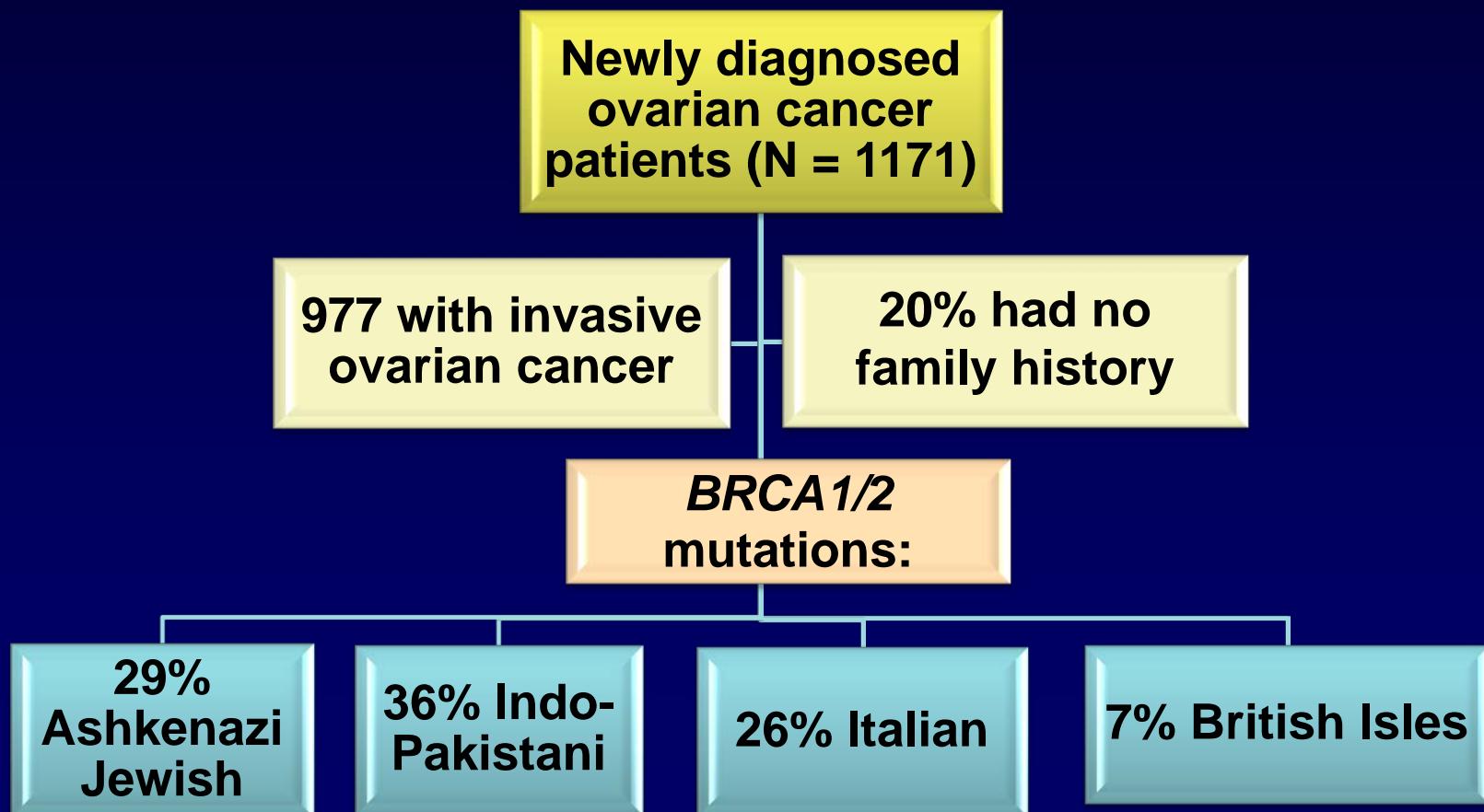
BRCA2 mutation carriers:

Breast cancer: 45% (31%–56%)
Ovarian cancer: 11% (2.4%–19%)

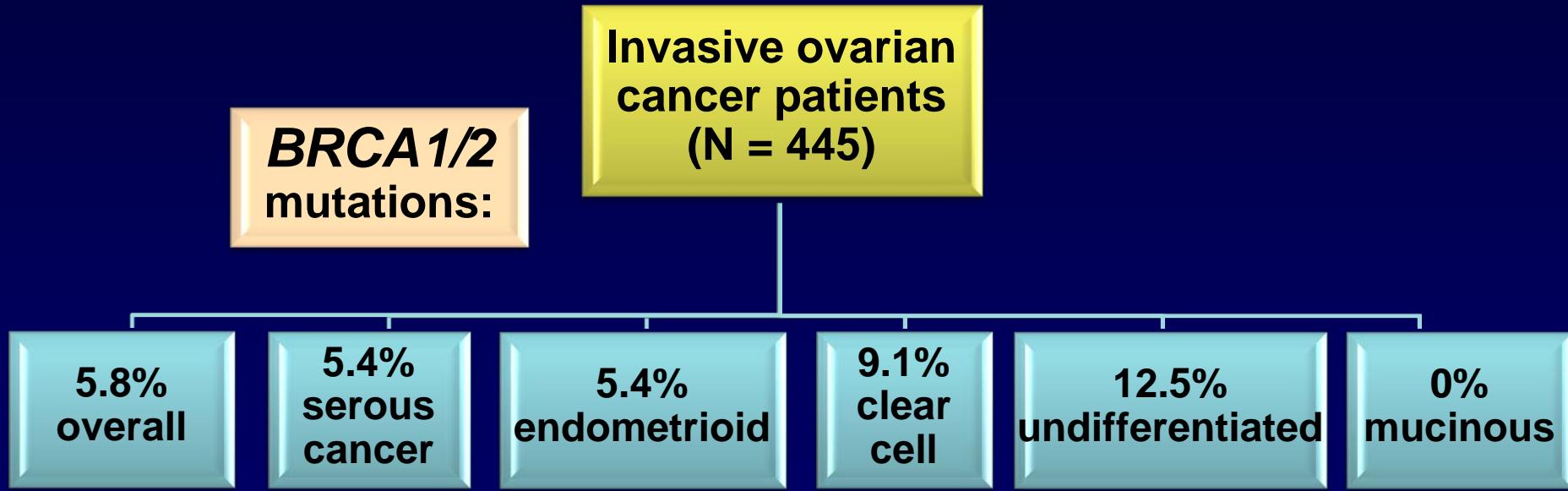
Canadian Study in Unselected Patients With Newly Diagnosed Ovarian Cancer



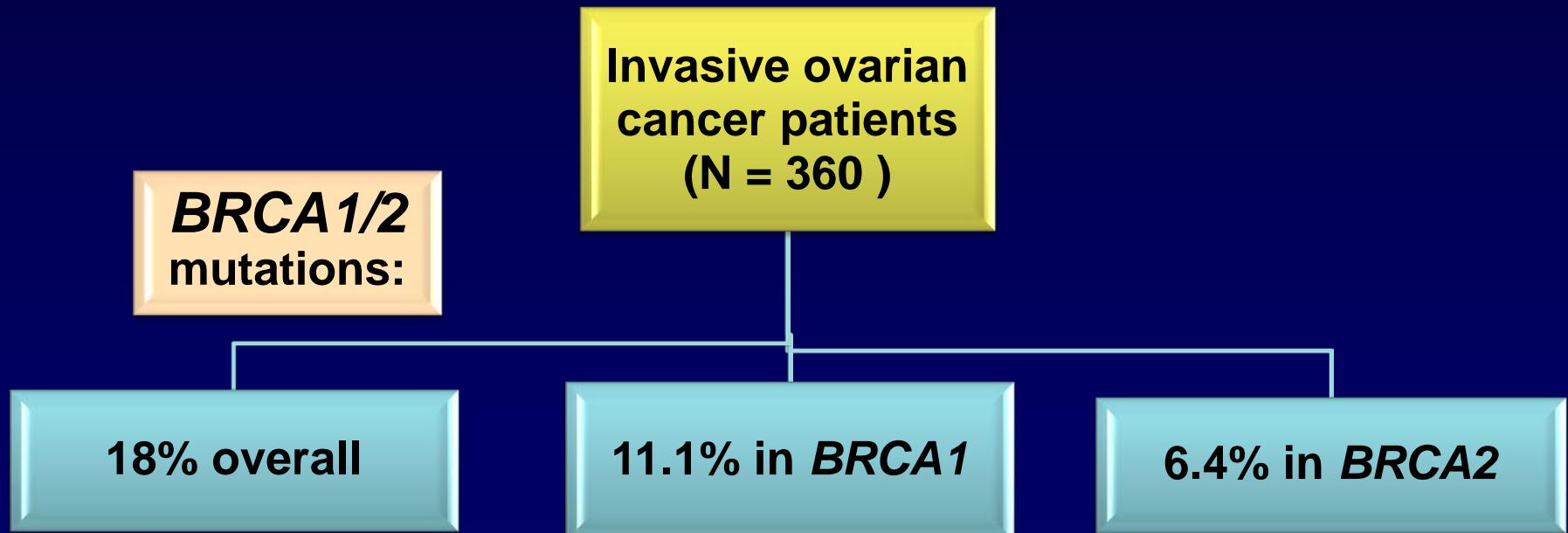
Canadian Study in Unselected Patients With Newly Diagnosed Ovarian Cancer



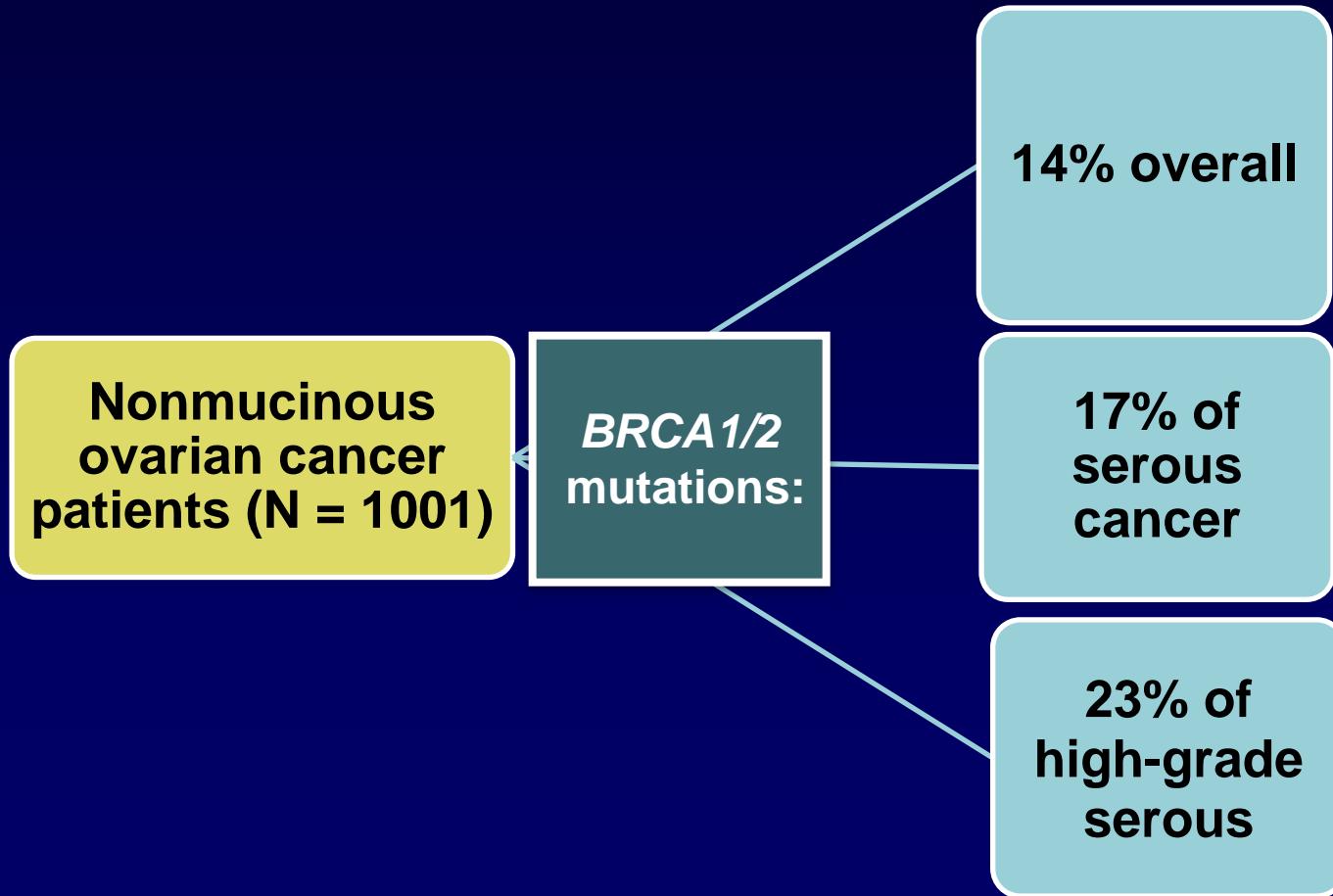
Danish Study in Population-Based Patients With Ovarian Cancer



US Study of Germline Mutations in Consecutive Cases of Invasive OC



Australian Population-Based Study of *BRCA1/2* Mutations in Ovarian Cancer



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

Endometrioid ovarian carcinoma (EC)

BRCA1/2 mutations in 8.4%
(10/119 women)

Clear cell carcinoma (CCC) or mixed CCC/serous

BRCA1/2 mutations in 6.3%
(4/63 women)

Carcinosarcomas

No patients
(out of 34)
identified as having
BRCA1/2 mutation

Is Age at Diagnosis a Predictor of a *BRCA1/2* Mutation?

	<i>BRCA1/2</i> mutation negative	<i>BRCA1</i> mutation positive	<i>BRCA2</i> mutation positive
Alsop et al ¹	60.5 y	53.4 y	59.8 y
Soegaard et al ²	61 y	49 y	
Jacobi et al ³	57.1 y	61.9 y	
Risch et al ⁴	55.6 y	51.2 y	57.5 y

~25% of *BRCA1/2* mutation carriers
are diagnosed >60 years

1. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663.
2. Soegaard M , et al. *Clin Cancer Res.* 2008;14(12):3761-3767.
3. Jacobi CE, et al. *Genet Med.* 2007;9:173-179.
4. Risch HA, et al. *Am J Hum Genet.* 2001;68(3):700-710.

Is Family History a Predictor of a *BRCA 1/2* Mutation?

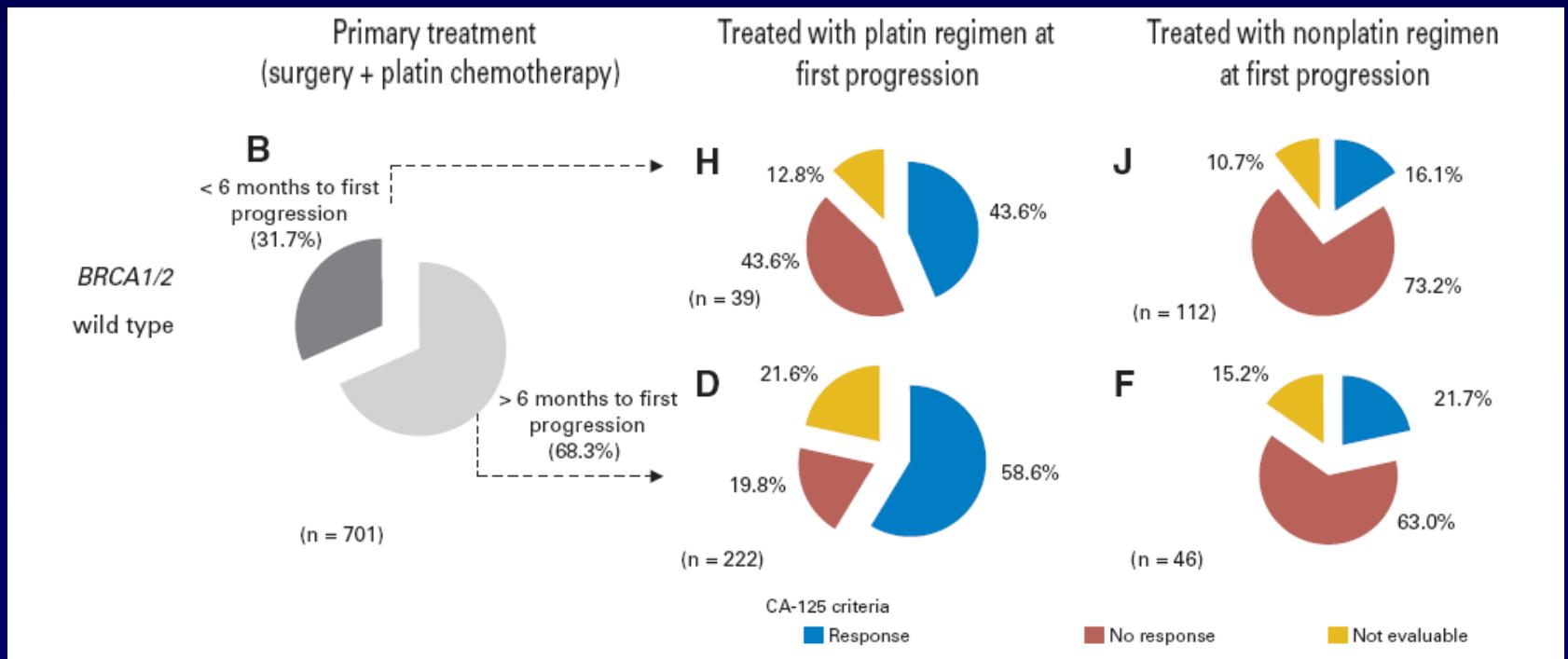
Absence of Family History (Breast/Ovarian) Among *BRCA* Mutation Carriers

Walsh et al ¹	30%
Alsop et al ²	44%
Soegaard et al ³	54%
Malander et al ⁴	10%
Jacobi et al ⁵	20%
Risch et al ⁶	20%

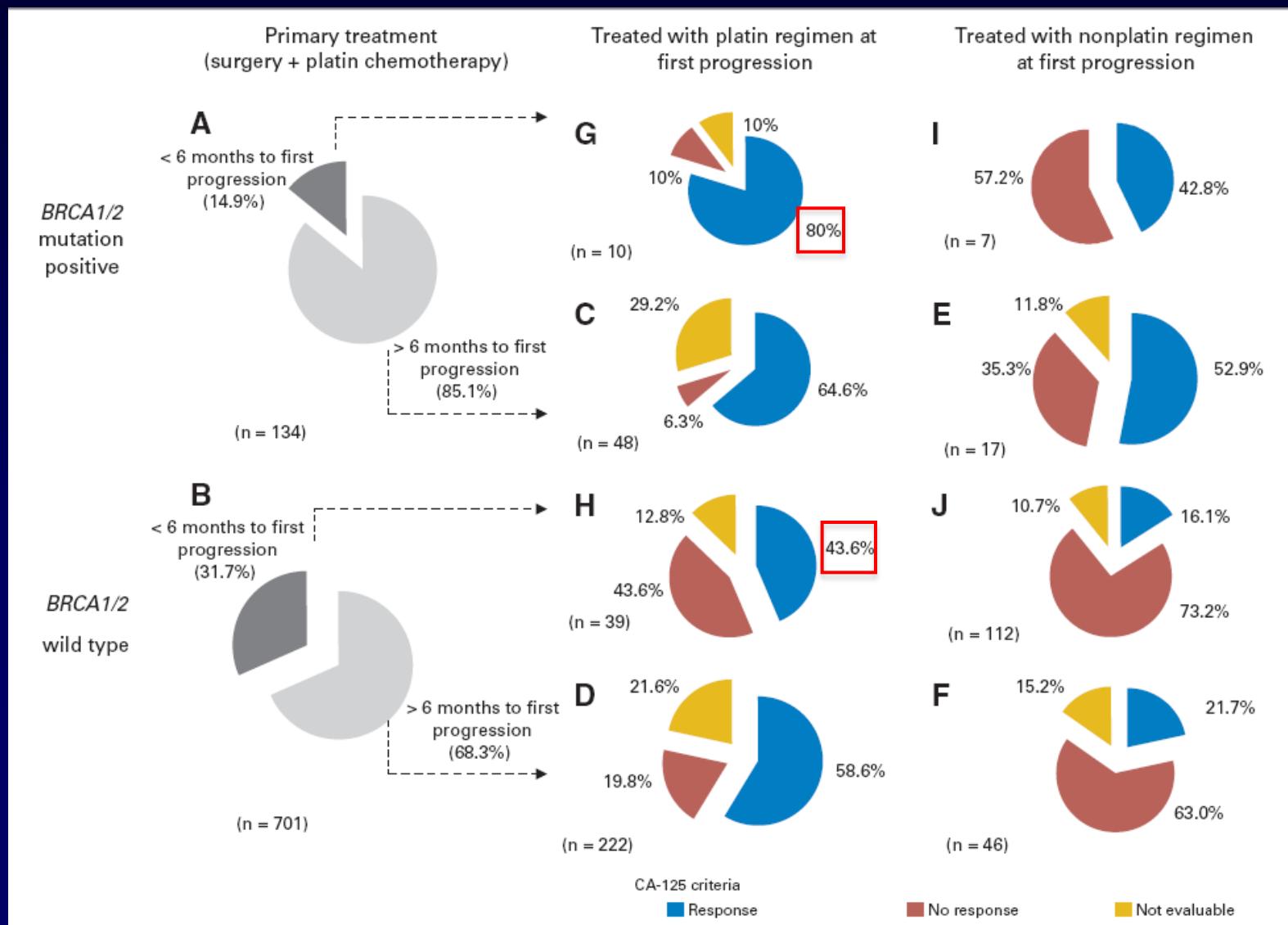
~30% of *BRCA 1/2* mutation carriers
do not have a family history

1. Walsh T, et al. *Proc Natl Acad Sci U S A.* 2011;108(44):18032-18037.
2. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663.
3. Soegaard M , et al. *Clin Cancer Res.* 2008;14(12):3761-3767.
3. Jacobi CE, et al. *Genet Med.* 2007;9:173-179.
4. Malander S, et al. *Eur J Cancer.* 2004;40(3):422-428.
5. Risch HA, et al. *Am J Hum Genet.* 2001;68(3):700-710.

Might Platinum Response Be Predictor of Germline *BRCA1/2* Mutation?



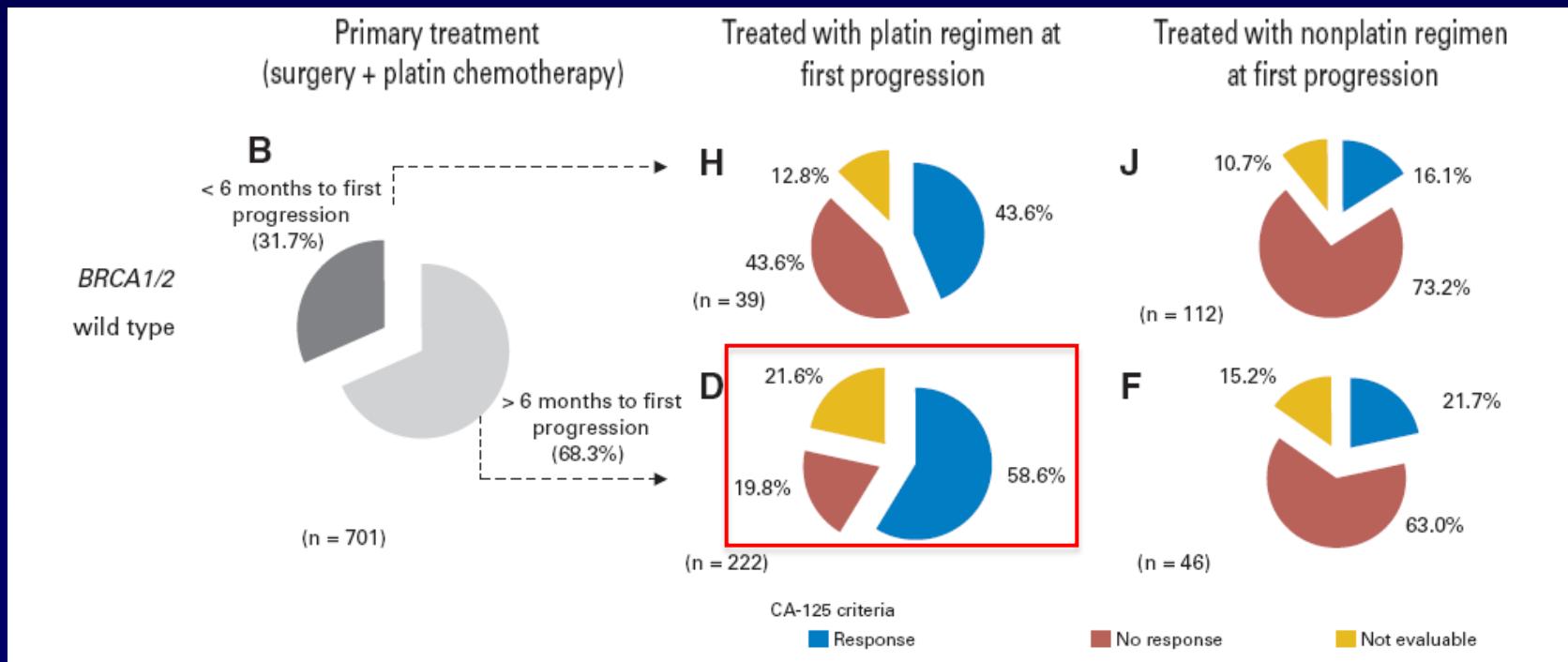
Might Platinum Response Be Predictor of Germline *BRCA1/2* Mutation?



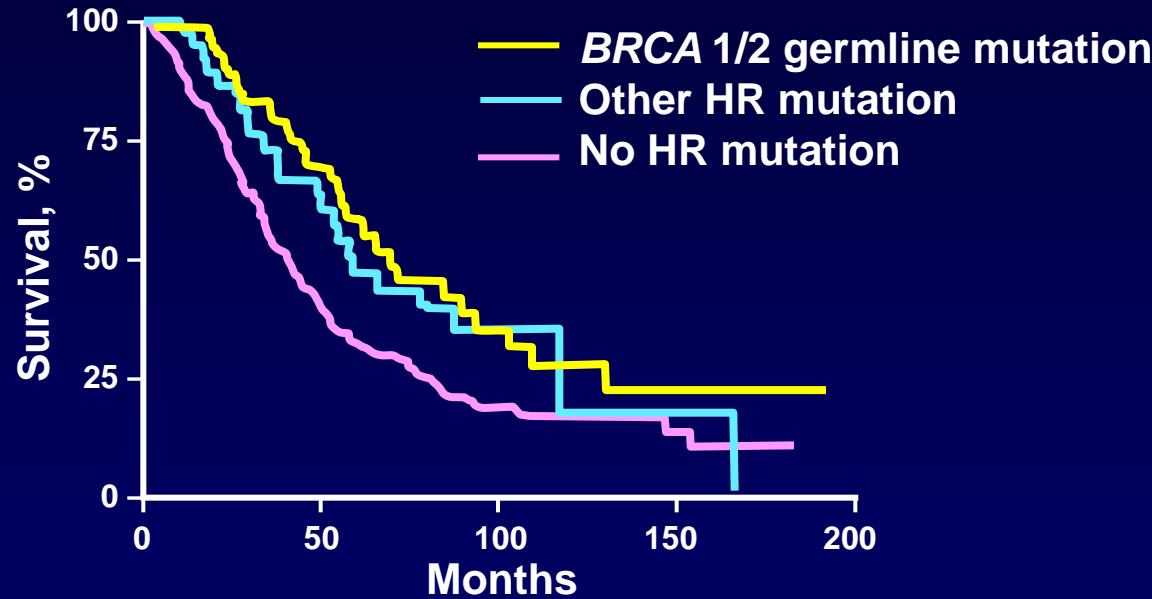
Might Ongoing Platinum Response Be Predictor of Somatic *BRCA1/2* Mutation?

98 of 700 women WT for germline *BRCA1/2* received a 3rd platinum regimen,
37 (38%) responded to 3rd platinum regimen
Fresh frozen tumor available for 16 of 37 cases:

4 tumors (25%) had a pathogenic somatic mutation



Might Platinum Response Be Predictor of Germline *BRCA1/2* Mutation?



Germline *BRCA1/2* mutations: improved OS **compared with subjects without HR mutations** (median 70 vs 41 mo; $P = .001$; HR, 0.5; 95% CI, 0.4–0.8)

Germline mutations in HR genes other than *BRCA1/2* or any HR somatic mutation (incl *BRCA1/2*) had improved OS (median 59 mo; $P = .05$; HR, 0.7; 95% CI, 0.5–1.0).

HR, homologous recombination

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

BRCA1/2 mutation status is prognostic in HGSC; associated with improved survival following platinum based therapy

Stratification by *BRCA1/2* status

Stratified randomization: to provide greater assurance that compared groups are **similar with respect to known prognostic features** other than treatment
Especially for small trials (eg 100 patients)

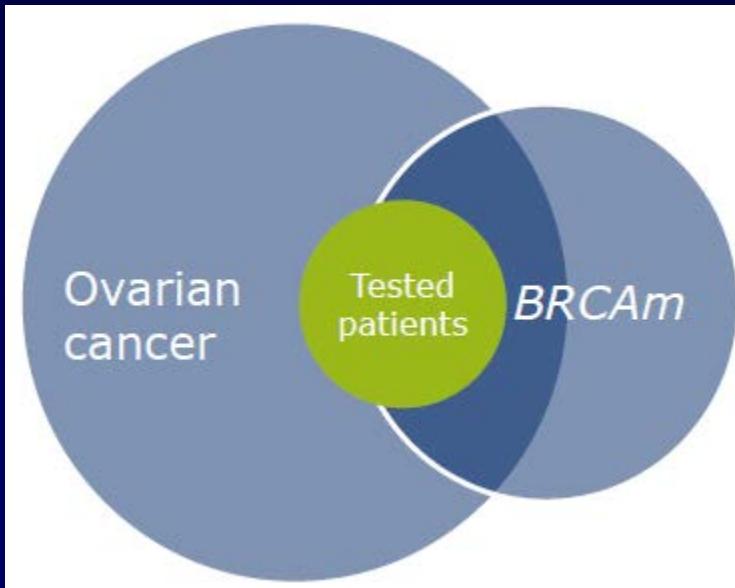
As trial size ↑ the risk for randomization-associated imbalances ↓

- **harmless** because it will not cause greater imbalance in the distribution of stratification factors among treatment groups than would be expected by chance in a nonstratified scheme.
- **frequently useful:** can reduce both types I and II error, improve trial efficiency and facilitate both subgroup analysis and interim analyses.
- **Important:**
 - small trials in which treatment outcome may be affected by known clinical factors that have a large effect on prognosis,
 - large trials when interim analyses are planned with small numbers of patients, and
 - trials designed to show the equivalence of two therapies.

Guidelines for use and reporting of stratified randomization in clinical trials

1. For superiority trials that seek to demonstrate the superiority of one therapy over another, consider stratified randomization when the overall sample size for a trial is small (<200 patients per treatment arm) **or when interim analyses or subgroup analyses** are planned that will involve small samples of a larger cohort.
2. Stratification is probably unnecessary for large superiority trials (>200 patients per treatment arm) that will not involve interim or subgroup analyses
3. For active control equivalence trials that seek to demonstrate the equivalence of compared therapies, consider stratified randomization even for very large sample sizes
4. When planning an active control equivalence trial (but not a conventional trial), sample size estimates should be adjusted for stratified randomization
5. **Choose stratification factors that identify groups with large differences in outcome rates.**

BRCA1/2 Testing Among High-Grade Ovarian Cancer Patients



6%-14% of unselected patients with an epithelial OC may carry a *BRCA1/2* mutation

Older age at diagnosis or lack of family history BC/OC does not exclude the presence of a germline *BRCA1/2* mutation

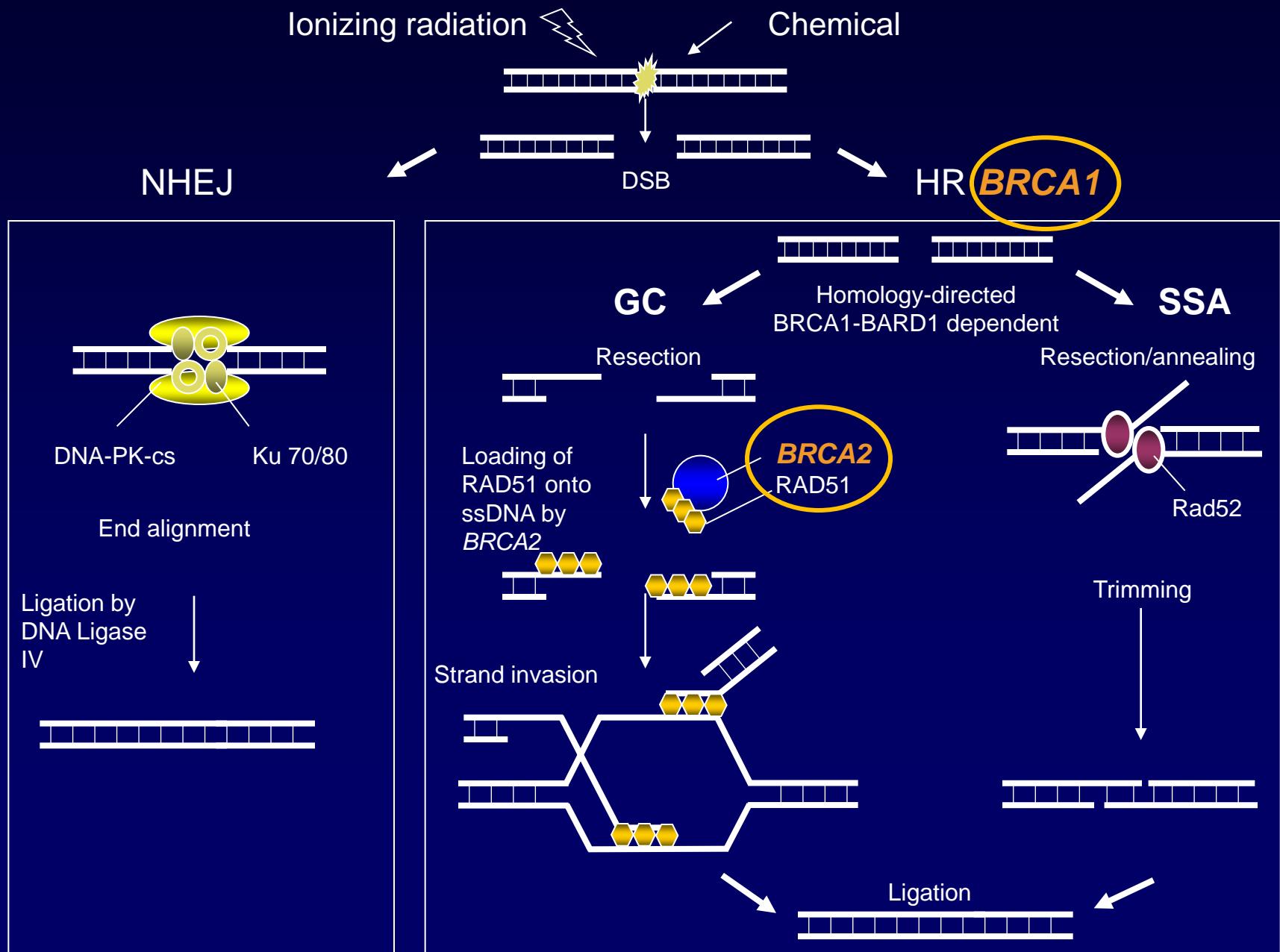
Recent Recommendations for Genetic Testing of Ovarian Cancer

- Australian EviQ national guidelines (May 2014):
 - an isolated **high-grade** (grades 2 & 3) **invasive nonmucinous ovarian**, fallopian tube, or primary peritoneal cancer, \leq age 70 yrs
 - OR invasive nonmucinous ovarian, fallopian tube, or primary peritoneal cancer at any age and a family history of BC or OC
- NCCN (US) (V1, February 2014):
 - individuals with a personal **history of OC** (including fallopian tubes and primary peritoneal cancer)
- SGO (October 2014):
 - offer genetic counseling and testing to **all women with OC**, fallopian tube, and peritoneal carcinoma
- ESMO (2013):
 - Unclear for women with OC without family history or relevant ethnic background**; becoming more important with new treatments emerging specifically for *BRCA1/2*-related cancers

Impact of *BRCA1/2* Mutations on Ovarian Cancer Treatment

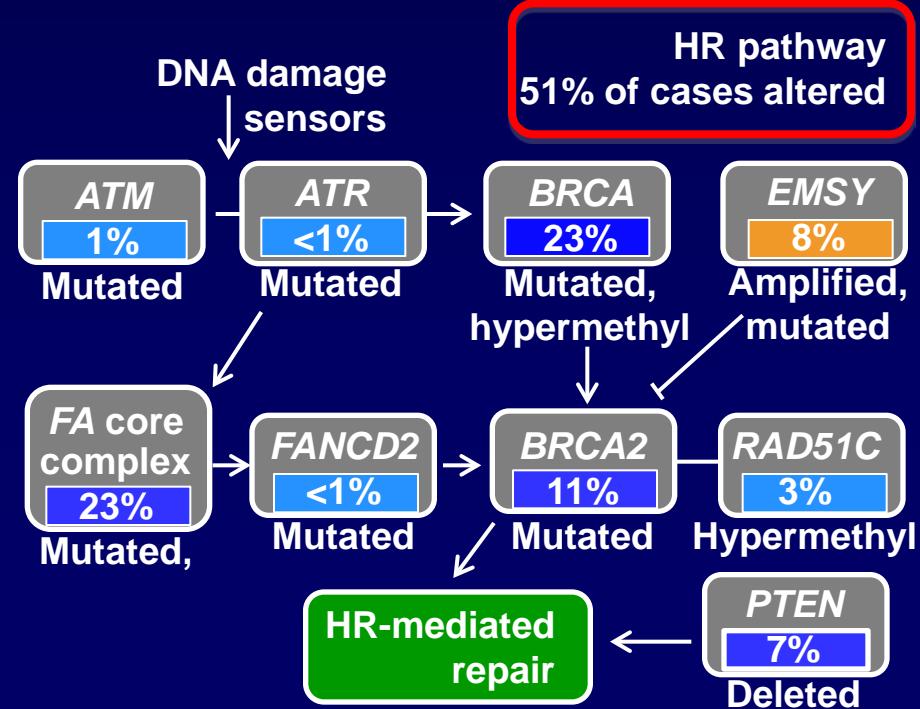
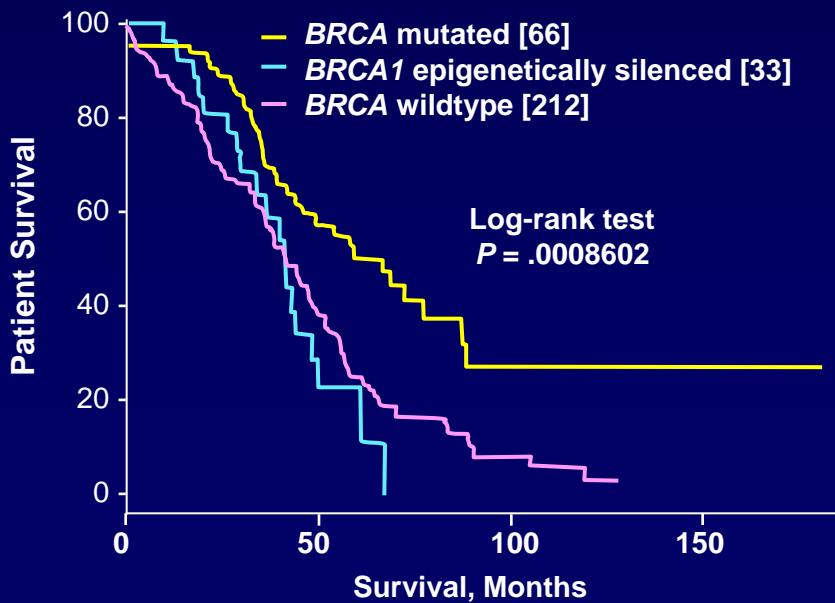
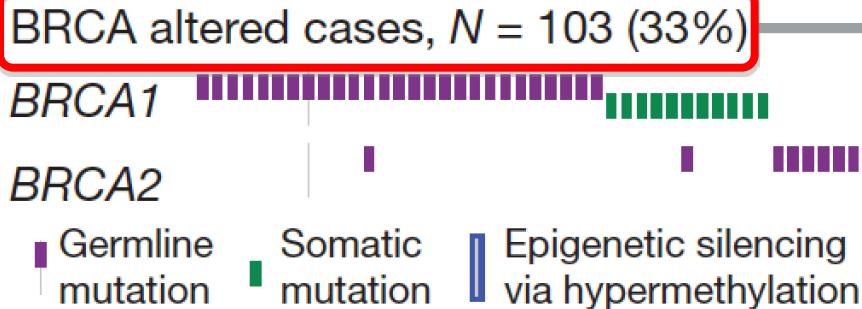
- What do *BRCA1* and *BRCA2* do?
- How can we exploit *BRCA1/2* deficiency?
- Beyond *BRCA1/2*?
- Implications for the clinic

BRCA1/2 and DNA Repair by Homologous Recombination



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

BRCA mutations:
17% germline
3% somatic

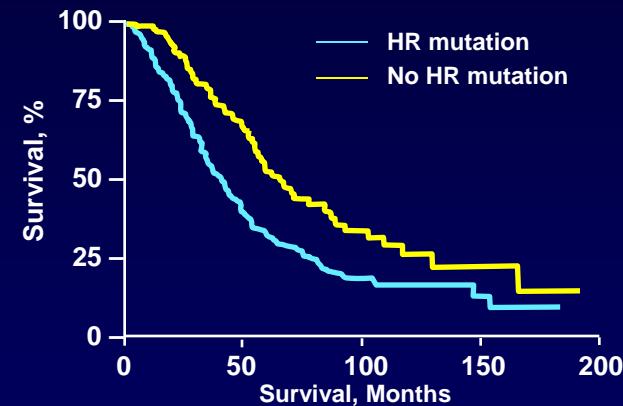
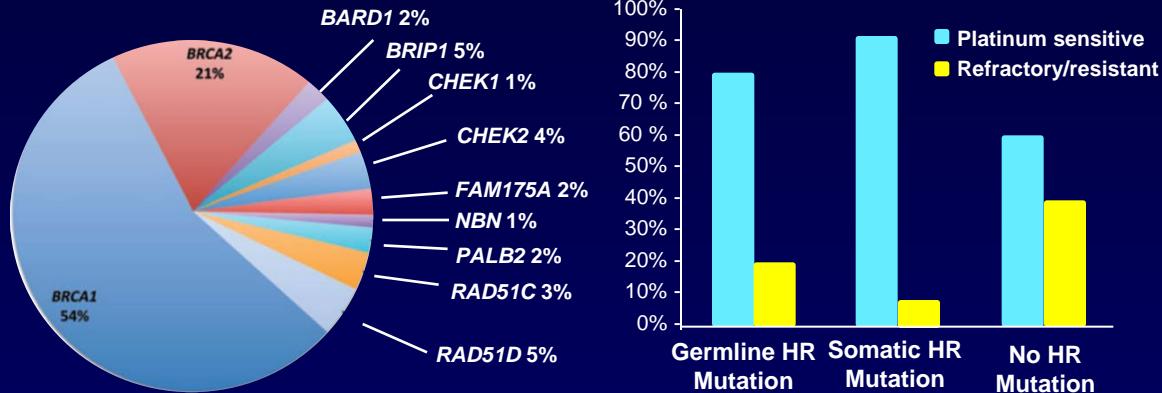


TCGA, The Cancer Genome Atlas

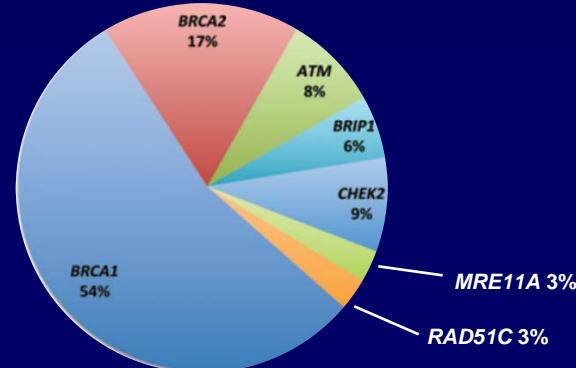
Cancer Genome Atlas Network Research. *Nature*. 2011;474(7353):609-615.

Germline and Somatic Loss-of-Function Mutations in Genes in the FA–BRCA Pathway Predict Higher Rates of Platinum Sensitivity and Better OS in Primary OC

Germline HR Mutations



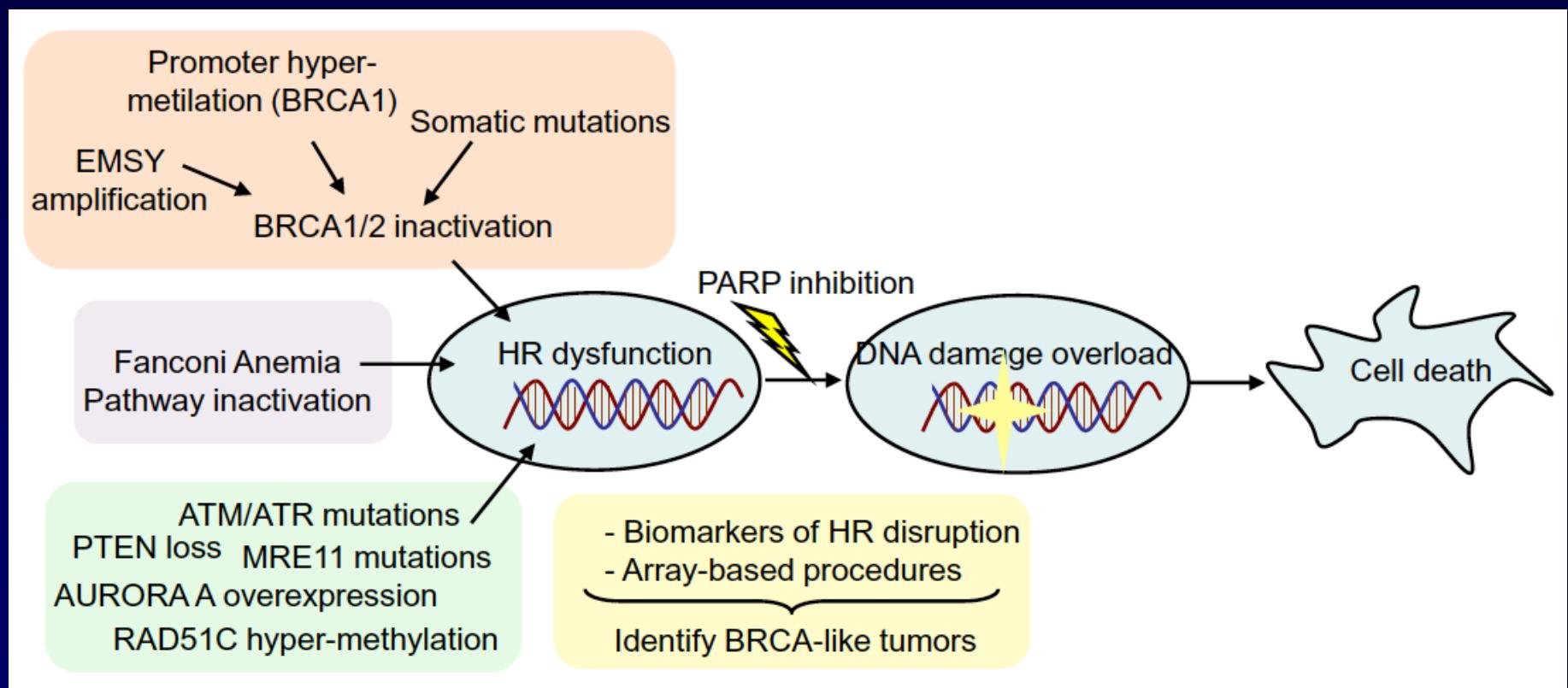
Somatic HR Mutations



An HR gene mutation was associated with an improved OS compared with cases without HR mutations (median OS 66 vs 41 months, $P = .006$; HR 0.6; 95% CI 0.4–0.8)

Importantly, somatic *BRCA1/2* mutations and germline and somatic mutations in HR genes other than *BRCA1/2* were also associated with improved survival and platinum sensitivity ($P = .05$).

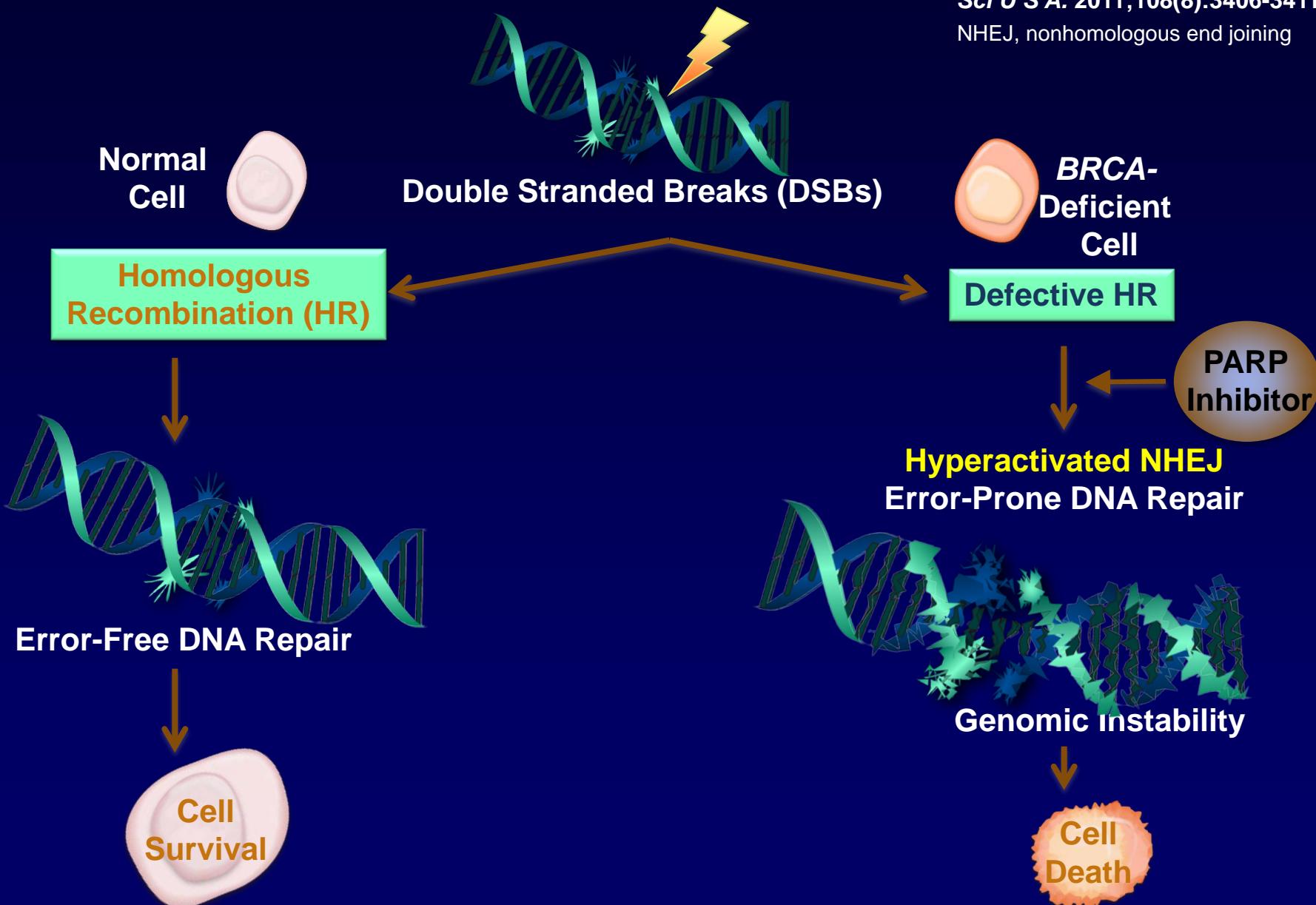
PARP Inhibitor Therapy in OC



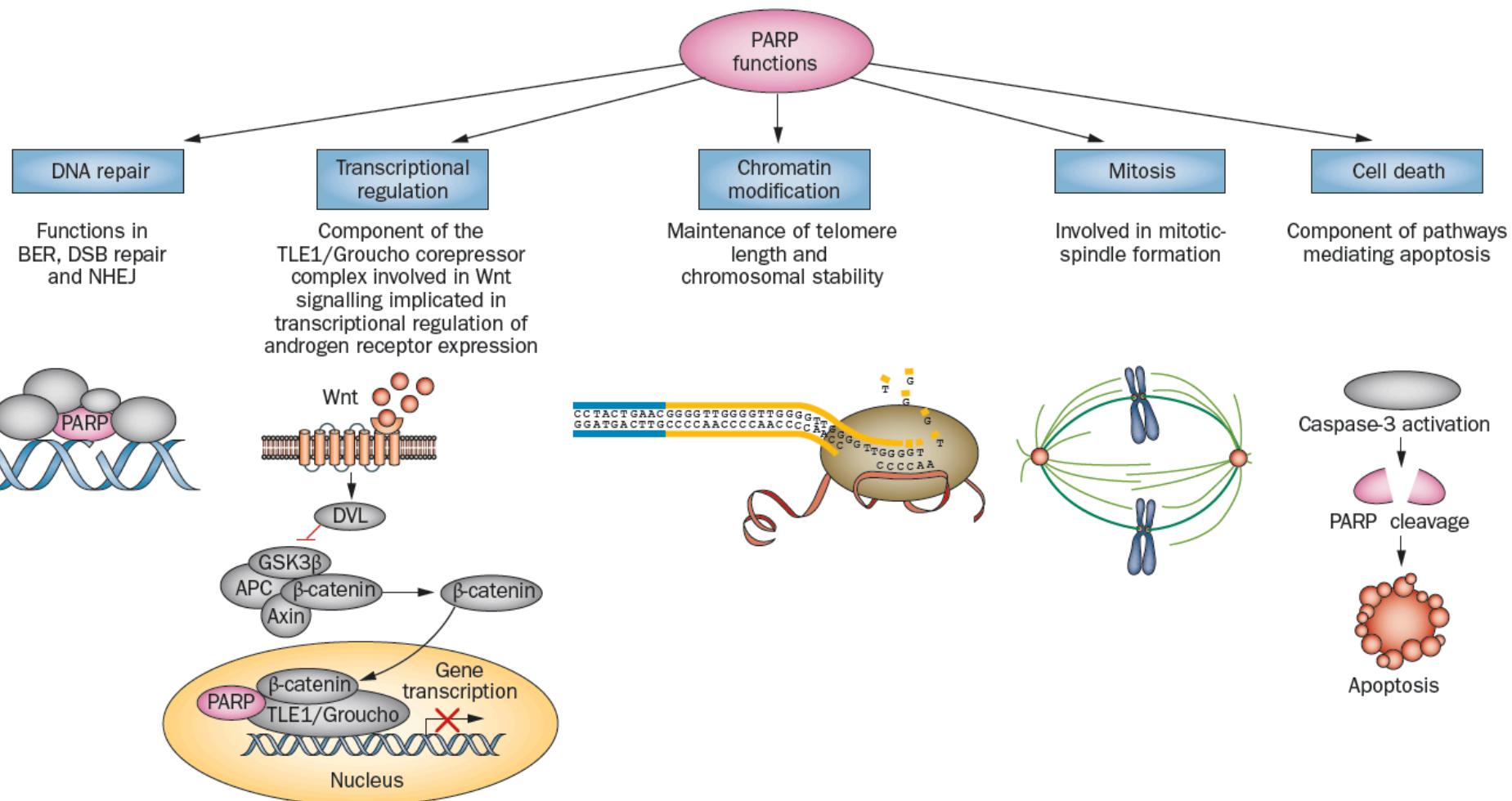
NHEJ Drives PARPi-Induced Genomic Instability

DNA Damage

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



PARP Inhibitors: For DNA-Repair Defective OC, How Else Might They Contribute to Cell Death?



The Range of PARP Inhibitors in Clinical Use and Development

PARP Inhibitor	Company	Target PARP	Route of Administration	Findings of key trials, if available, and/or phase of development
Olaparib (AZD2281)	AstraZeneca	PARP1/2/3	Oral	Series of phase II trials demonstrated efficacy in <i>BRCA</i> -mutation carriers; Currently being evaluated in the adjuvant setting in patients with TNBC
Veliparib (ABT-888)	Abbott Laboratories	PARP1/2	Oral	Acceptable safety profile and promising antitumor activity, especially in <i>BRCA</i> -deficient patients with ovarian cancer, was observed in a series of phase I trials; Phase II studies are ongoing
Rucaparib (AG-014, 699; CO-338)	Clovis Oncology	PARP1/2	Oral or intravenous	Currently being evaluated in a phase II/III study in <i>BRCA</i> -mutation carriers with mBC or advanced-stage ovarian cancer
BMN-673	BioMarin Pharmaceutical	PARP1/2	Oral	Has shown impressive antitumor activity in patients with <i>BRCA</i> mutations; Currently, phase II-III studies in patients with germline <i>BRCA</i> mutations are ongoing
CEP-9722	Teva Pharmaceutical Industries	PARP1/2	Oral	Clear evidence of PARP inhibition has been demonstrated in preclinical studies, and early studies in patients
Niraparib (MK4827)	Merck	PARP1/2	Oral	Phase I-II studies have revealed antitumor activity, especially in patients with germline <i>BRCA</i> mutations; At present, phase II-III studies in such patients are ongoing

mBC, metastatic breast cancer; PARP, poly(ADP-ribose) polymerase; TNBC, triple-negative breast cancer

Clinical trials also underway to determine response of non-*BRCA*1/2 mutant OC to PARP inhibitors

Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2014 Oct 7. [Epub ahead of print].

Impact of *BRCA1/2* Mutation

Family implications
Risk-reduction

High-grade epithelial
OC (*nonmucinous*)
BRCA1/2 mutation

Follow-up:
Breast cancer surveillance

Information about
clinical outcome,
improved response
to therapy

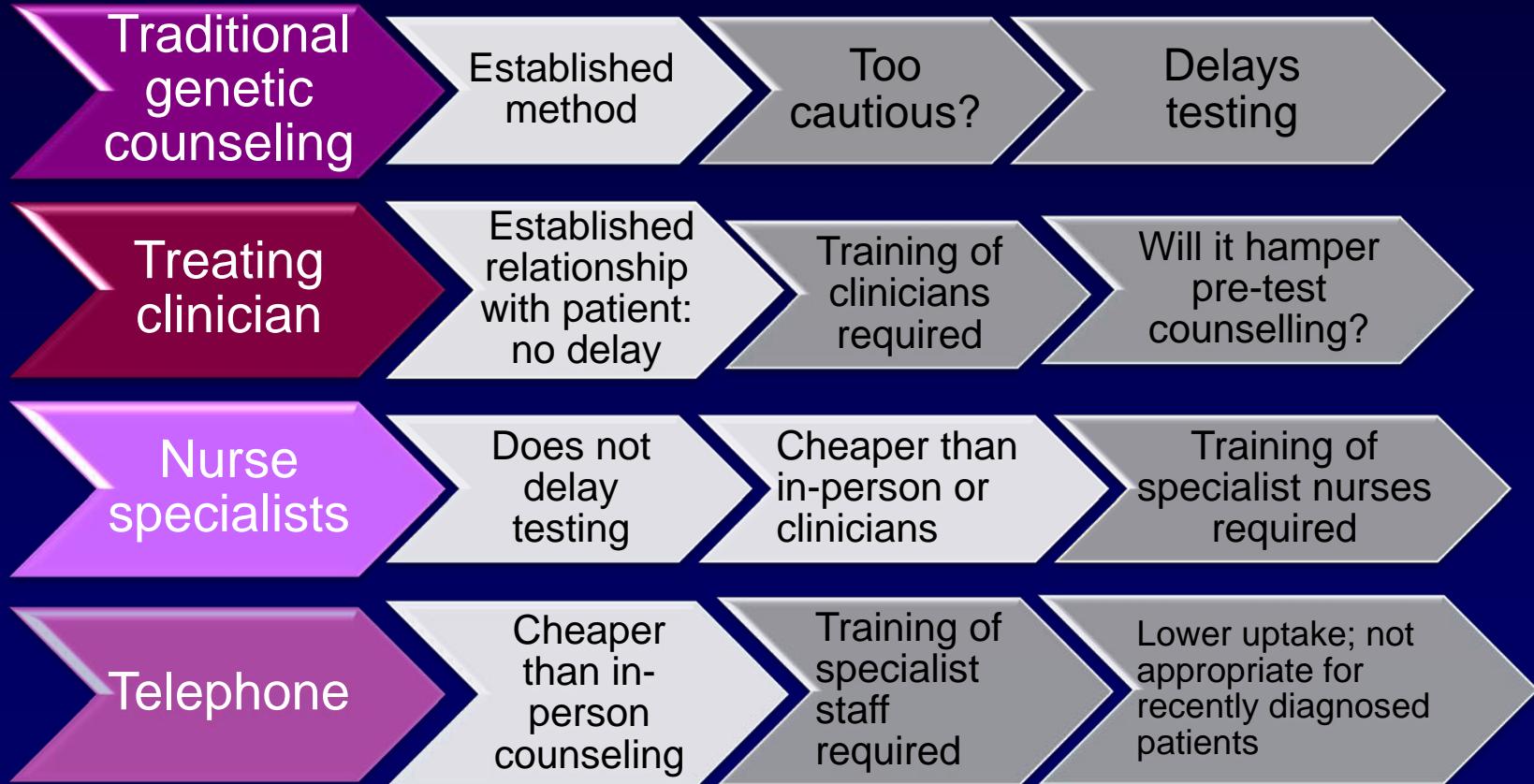
Treatment options:

- Rechallenge with platinum
- PARP inhibitors
- Immune modulation
- Other

How *BRCA1/2* Testing May Change With the Introduction of *BRCA1/2*-Directed Therapies

- More patients are being referred for testing
- Quicker results are needed
- Testing may take place earlier at first diagnosis/treatment
- Treatment-focused genetic testing:
deals with medical implications
less focus on familial implications until later

Genetic Counseling Models



prIME POINTS™

- >10% of high-grade epithelial nonmucinous OC associated with germline *BRCA1/2* mutations
- Somatic *BRCA1/2* mutations are identified in approximately 3%-7% of high-grade serous OC
- Around 1/3 of *BRCA1/2* carriers with OC do not have a family history of BC/OC, or were diagnosed >60yo
- Patients with invasive epithelial OC should be tested for *BRCA1/2* promptly because of implications for therapy and family

prIME POINTS™

- ✓ ***BRCA1/2-carriers with OC have better outcomes and are more sensitive to platinum-based chemotherapy and PARPi than noncarriers.***
- ✓ ***BRCA1/2-carriers with OC may be more sensitive to non-platinum-based chemotherapy***
- ✓ ***BRCA1/2 is not a conventional biomarker: multiple implications***



This activity is provided
by prIME Oncology.

ADDING PRECISION AND POWER TO PROGRESS IN OVARIAN CANCER MANAGEMENT