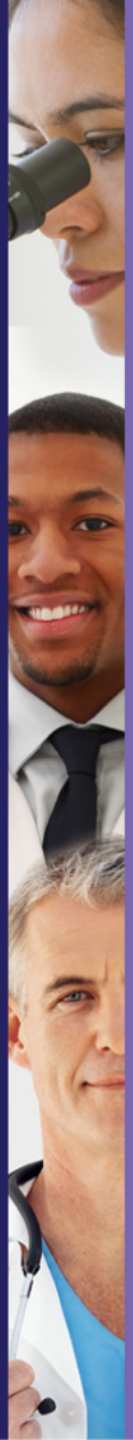
National Cancer Institute

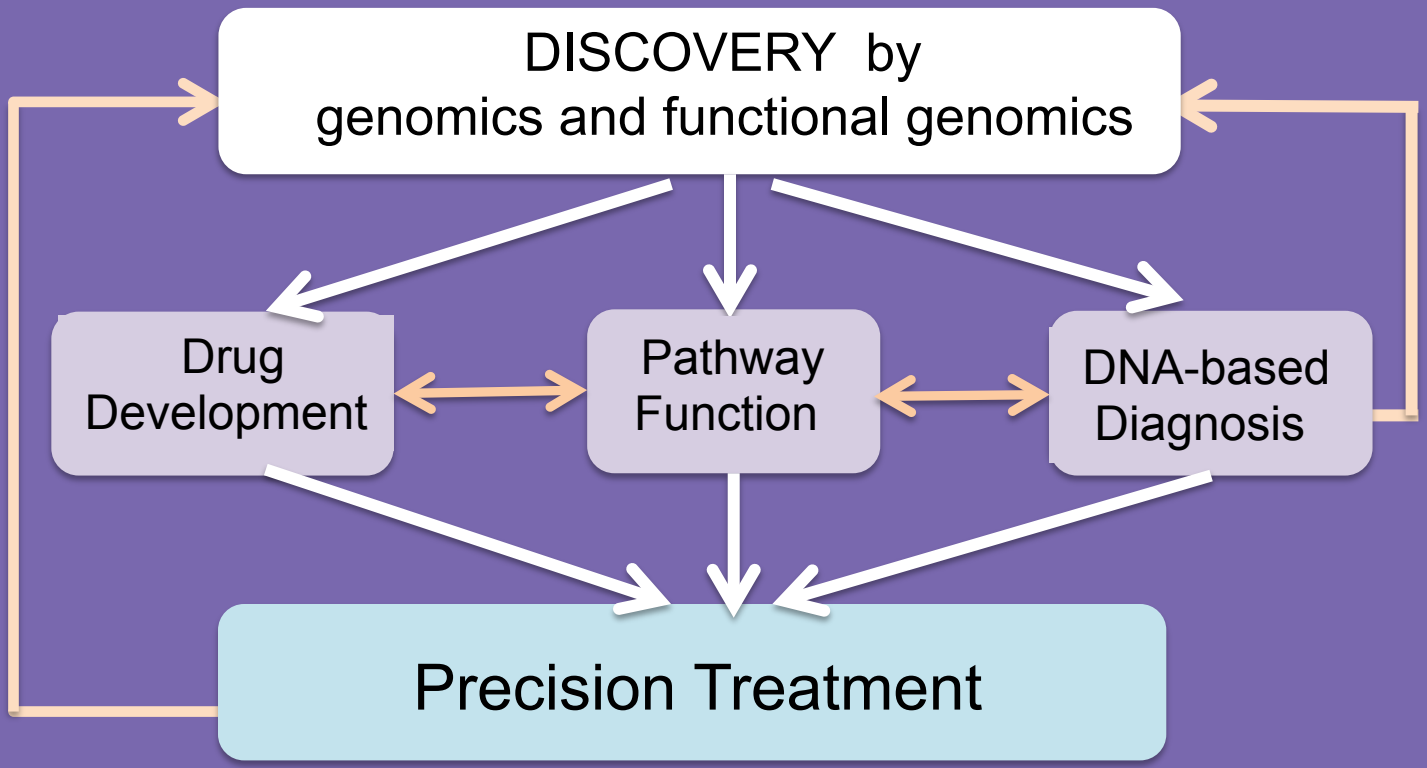


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

NCI Center for Cancer Genomics

Mission: To develop and apply cutting-edge genome science to improve cancer prevention, care and detection



Future of Cancer Genomics: What next in 2014?

- Plan next steps within next 3-6 months
  - Because *at least* 8-10 months from decision to genomic analyses
- Strategic use of lessons learned from TCGA
- Capitalize on success of TCGA structure
- Continue partnership between NCI & NHGRI

Cancer Genomics Beyond 2013

- Build upon Strengths of TCGA Pipelines
  - Processing & Genomic Characterization
  - Analytical Tools
  - Data Sharing
- Hybrid of projects
  - Top-down
  - Bottom-up
- Plan major transition towards clinics
- Retain emphasis on discovery

Questions of 2012 that will shape the future of NCI-supported Cancer Genomics

- Unraveling cancer biology
  - Drivers vs. Mutations
    - Somatic Molecular Epidemiology
    - Large studies drawn from different study designs
  - Clonality and Progression
    - High coverage

Questions of 2012 that will shape the future of NCI-supported Cancer Genomics

- Value of epidemiology/germline
  - Risk
    - Individual
    - Public Health
    - Contribution to somatic events
  - Treatment Stratification
  - Pharmacogenomics
    - Response
    - Toxicity
    - Outcome)

“Genome-related” Trials: More & Better

1. Genome - INFORMED trials

DNA information obtained during or after trial closes

Value of prospective collection from trials

2. Genome- DRIVEN trials

Sequencing/Characterization to guide treatment

- ALKEMIST
- EXCEPTIONAL CASES

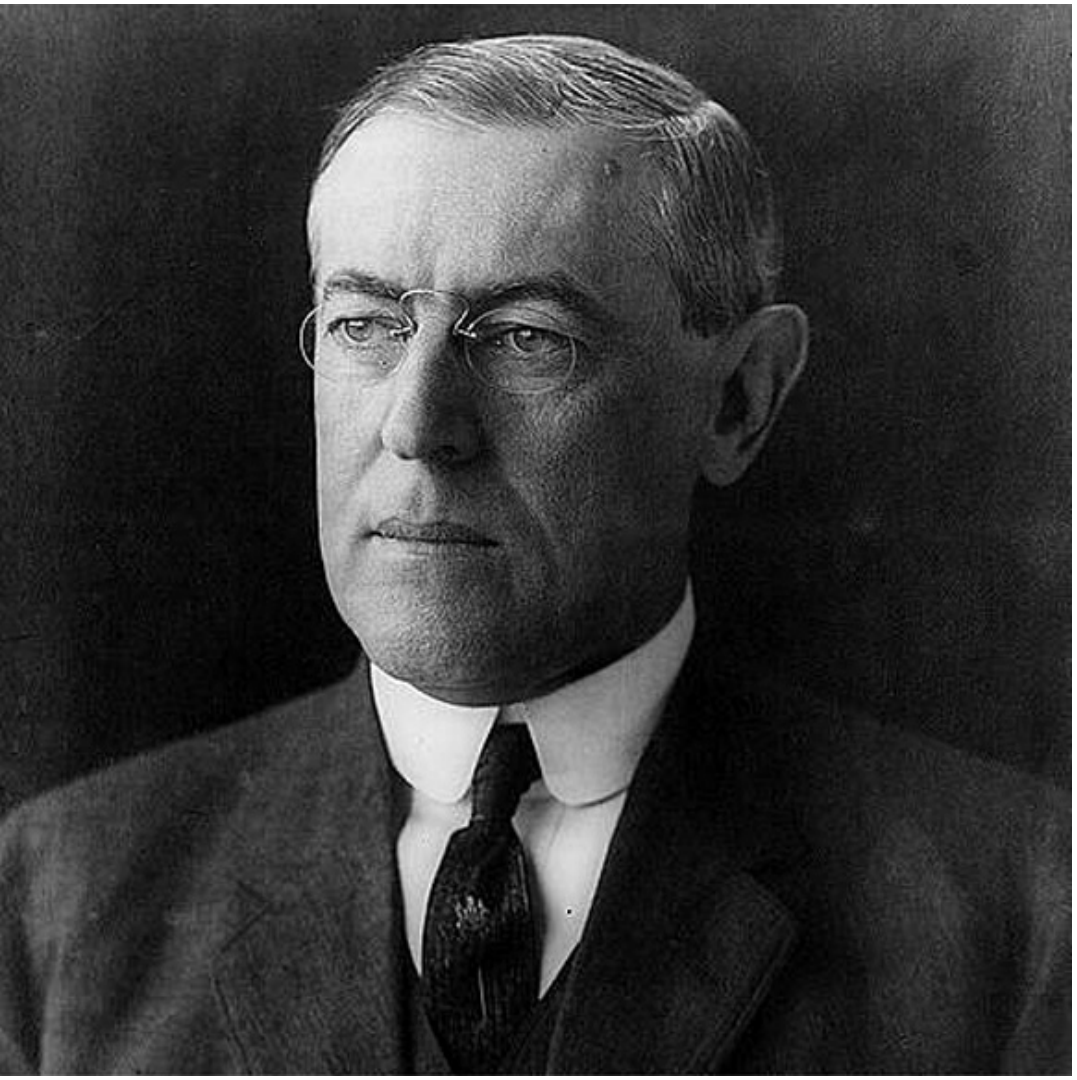
3. Genomic Analysis not as part of a trial

Archived samples for discovery

Gene-environment analyses

Current TCGA Goals

- Achieve milestones per cancer site
  - Timely publications
- Conduct PanCan analyses
- Forge new solutions to issues related to Data:
  - Integration
  - Storage
  - Sharing
- Fortify collaborative spirit



Advances will be accelerated by "Collective Intelligence"

"I not only use all of the brains I have, but all I can borrow"

Woodrow Wilson

TCC ysis

- Testin
- Prelim
- Possib
  - Cons trials

ORIGINAL CONTRIBUTION

Association of *BRCA1* and *BRCA2* Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer

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Kenneth Hess, PhD
Ilya Shmulevich, PhD
Anil K. Sood, MD
Wei Zhang, PhD

Context Attempts to determine the clinical significance of *BRCA1/2* mutations in ovarian cancer have produced conflicting results.

Objective To determine the relationships between *BRCA1/2* deficiency (ie, mutation and promoter hypermethylation) and overall survival (OS), progression-free survival (PFS), chemotherapy response, and whole-exome mutation rate in ovarian cancer.

Design, Setting, and Patients Observational study of multidimensional genomics and clinical data on 316 high-grade serous ovarian cancer cases that were made public between 2009 and 2010 via The Cancer Genome Atlas project.

Main Outcome Measures OS and PFS rates (primary outcomes) and chemotherapy response (secondary outcome).

Results *BRCA2* mutations (29 cases) were associated with significantly better OS (adjusted hazard ratio [HR], 0.33; 95% CI, 0.16-0.69; $P=.003$ and 5-year OS, 61% for *BRCA2*-mutated vs 25% for *BRCA* wild-type cases) and PFS (adjusted HR, 0.40; 95% CI, 0.22-0.74; $P=.004$ and 3-year PFS, 44% for *BRCA2*-mutated vs 16% for *BRCA* wild-type cases), whereas neither *BRCA1* mutations (37 cases) nor *BRCA1* methylation (33 cases) was associated with prognosis. Moreover, *BRCA2* mutations were associated with a significantly higher primary chemotherapy sensitivity rate (100% for *BRCA2*-mutated vs 82% [$P=.02$] and 80% [$P=.05$] for *BRCA* wild-type and *BRCA1*-mutated cases, respectively) and longer platinum-free duration (median platinum-free duration, 18.0 months for *BRCA2*-mutated vs 11.7 [$P=.02$] and 12.5 [$P=.04$] months for *BRCA* wild-type and *BRCA1*-mutated cases, respectively). *BRCA2*-mutated, but not *BRCA1*-mutated cases, exhibited a "mutator phenotype" by containing significantly more mutations than *BRCA* wild-type cases across the whole exome (median mutation number per sample, 84 for *BRCA2*-mutated vs 52 for *BRCA* wild-type cases, false discovery rate <0.1).

Conclusion Among women with high-grade serous ovarian cancer, *BRCA2* mutation, but not *BRCA1* deficiency, was associated with improved survival, improved chemotherapy response, and genome instability compared with *BRCA* wild-type.

JAMA. 2011;306(14):1557-1565 www.jama.com

INCREASED SURVEILLANCE OF *BRCA1/2* germ line mutation carriers is a generally accepted strategy for detecting early ovarian cancer. Women with *BRCA1* mutations have a 39% to 54% cumulative lifetime risk of developing ovarian cancer and women with *BRCA2* mutations have an 11% to 23% risk.[1-3]

Both *BRCA1* (NCBI Entrez Gene 672) and *BRCA2* (NCBI Entrez Gene 675) tumor suppressor genes are involved in DNA repair via homologous recombination. Cells with alterations in homologous recombination pathway genes are unable to repair DNA double-strand breaks by homologous recombination, which is mostly error free. This can result in genomic instability and a predisposition to malignant transformation.[4,5] Conversely, because homologous recombination pathway deficiencies can also impair tumor cells' ability to repair DNA cross-links introduced by chemotherapy agents such as cisplatin, it has been hypothesized that *BRCA*-deficient patients will likely have higher survival rates because of an improved response to platinum-based chemotherapy.[6]

For editorial comment see p 1597.

However, conflicting data exist regarding the outcome of *BRCA*-deficient patients after ovarian cancer develops. Some researchers have found that ovarian cancer patients with *BRCA1/2* germ line mutations have a more favorable

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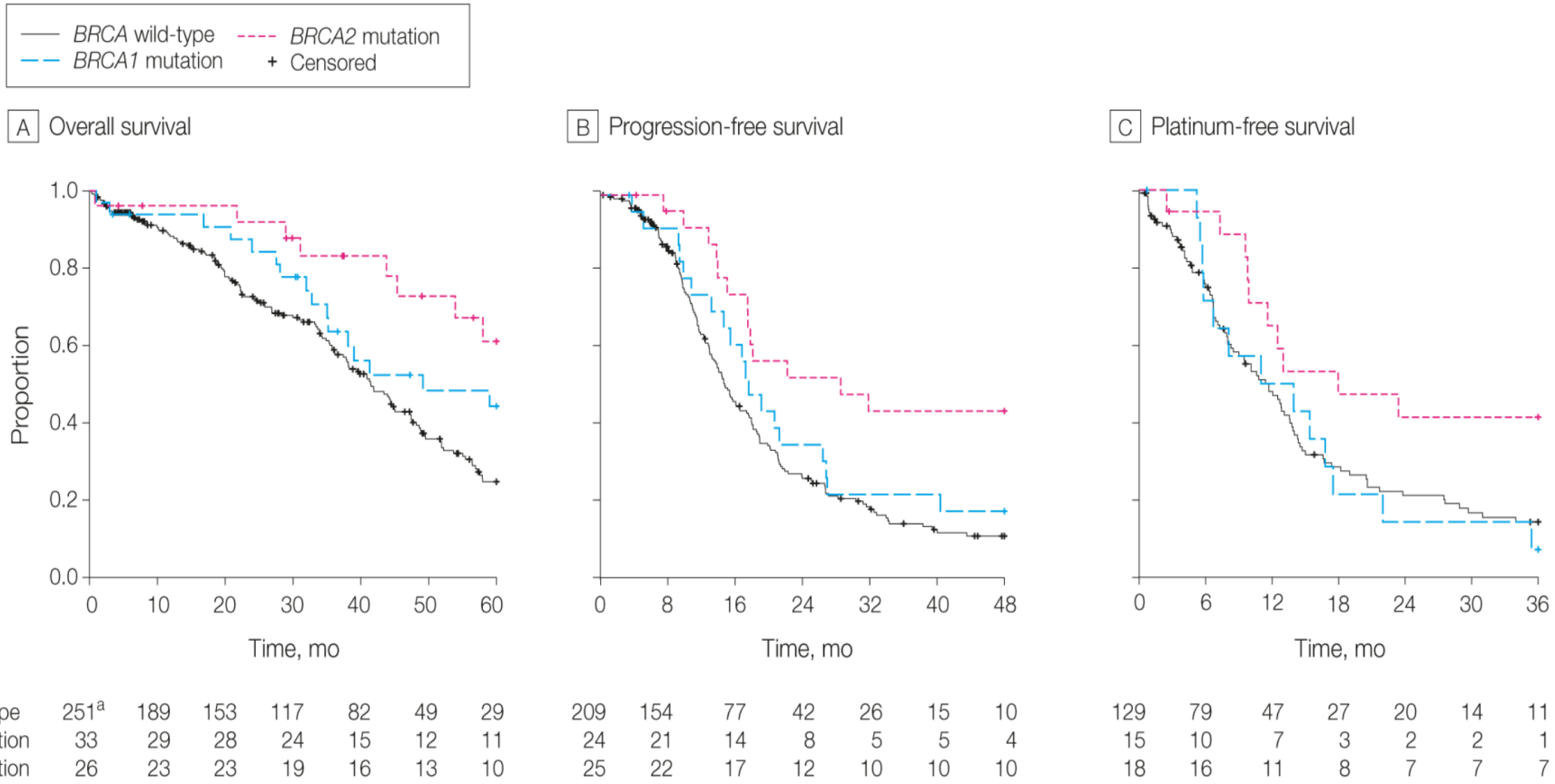
Corresponding Author: Wei Zhang, PhD, Unit 85, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (wzhang@mdanderson.org).

From: **Association of BRCA1 and BRCA2 Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer**

JAMA. 2011;306(14):1557-1565. doi:10.1001/jama.2011.1456



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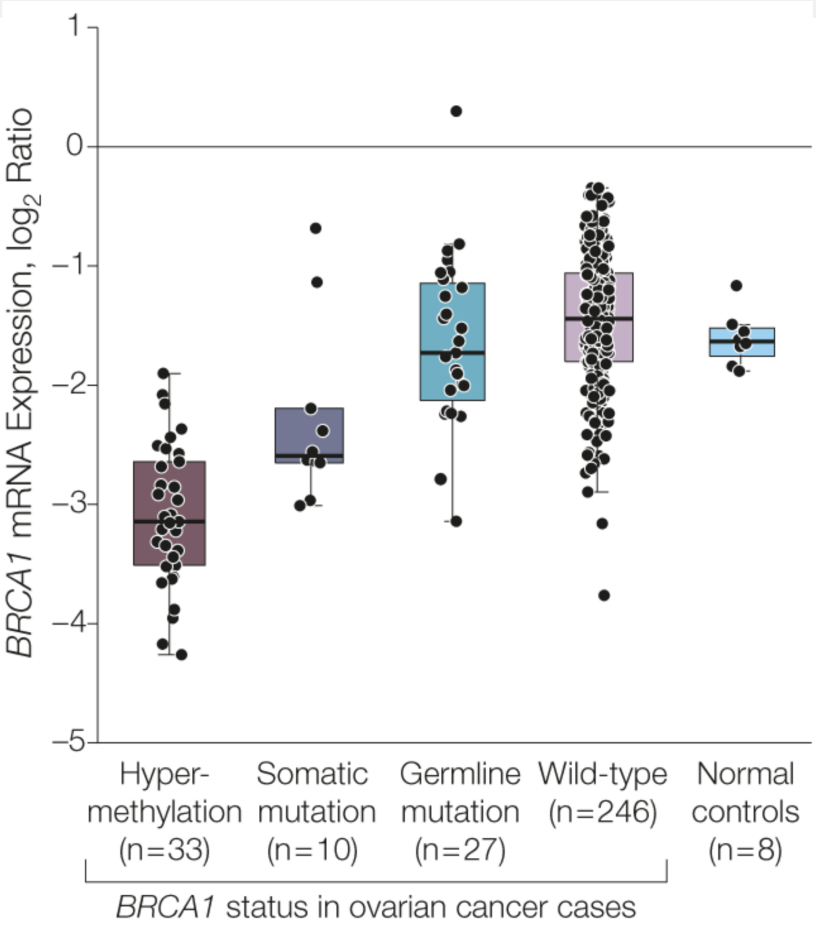


Follow-up Ovarian Cancer Outcome by BRCA Status

- Conduct large, multi-center study of EOC cases with and without *BRCA1/2* mutations
  - Improve estimates of survivorship based on germ-line BRCA status
  - Explore Genotype-Phenotype correlations for
    - *BRCA1* vs. *BRCA2*
    - Mutation class, location

Bolton et al JAMA 2012

Study Design

- **20 studies** from the US, UK, Australia, Europe, Israel and Asia.
- **3,824 EOC Cases**
  - 1,115 *BRCA1* carriers
  - 332 *BRCA2* carriers
  - 2,377 Non-carriers
- **Ascertainment**
  - Same for carriers and non-carriers
    - Family history of breast/EOC
    - Non-selected
- **Treatment information not available for all**
  - 95% of cases diagnosed post 1990 received platinum-based therapy
  - Analysis limited to cases who received platinum-based therapy **OR** diagnosed post 1990

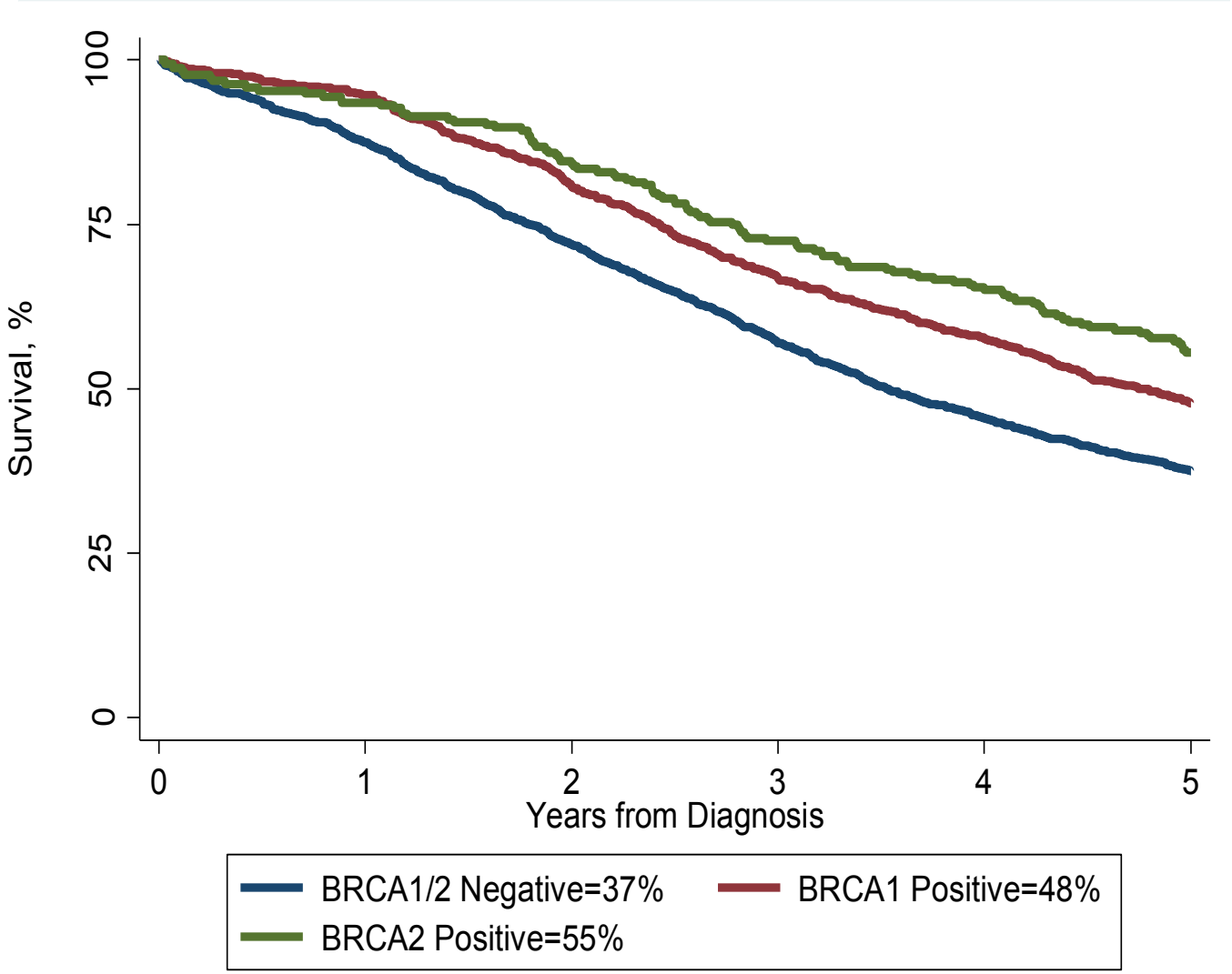
Bolton et al JAMA 2012

Five Year Overall Survival by *BRCA* Status

Non-carriers	36%
BRCA1	44%
BRCA2	52%

Average time for ascertainment- 9 months post diagnosis and under active follow-up for 50 months

Kaplan-Meier Cumulative Survival by *BRCA* Mutation Status



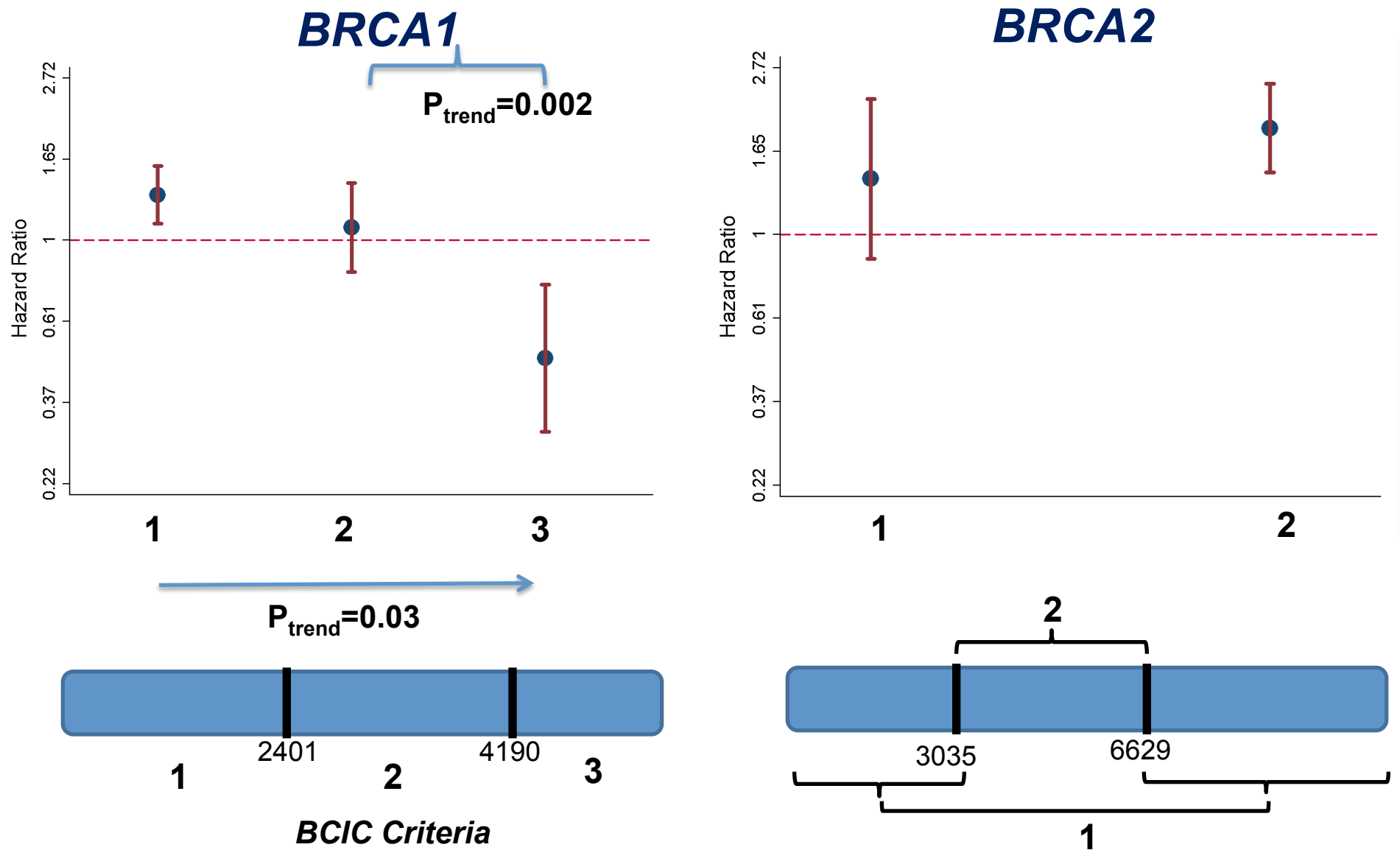
Residual Disease and Response to Platinum-based chemotherapy

- *BRCA1* and *BRCA2* carriers more likely than non-carriers to show favorable response to platinum-based therapy

Impact of adjustment for response to therapy

	Unadjusted		Adjusted	
	HR	P-value	HR	P-value
BRCA1 vs Non-Carriers (ref)	0.51(0.34-0.76)	0.001	0.57(0.37-0.86)	0.007
BRCA2 vs Non-Carriers (ref)	0.35(0.18-0.65)	0.001	0.43(0.23-0.81)	0.009

Adjusted Cox Regression by Mutation Location and not Class I/II



Summary and Conclusions

- *BRCA1* and *BRCA2* carriers show a substantially improved survival compared to non-carriers
- *BRCA2* carriers show a distinct clinical course from *BRCA1* carriers
- Preliminary evidence that survival varies by mutation location for *BRCA1*
- Implications for clinical trial design
  - Traditional therapies
  - Therapies targeted for *BRCA1/2* carriers