NCI Center for Cancer Genomics

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

DISCOVERY by genomics and functional genomics

Drug Development

Pathway Function

DNA-based Diagnosis

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

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Sofia Khan, PhD
Yan Sun, MD, PhD
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 genomic 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 <.01).

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.

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

For editorial comment see p 1597.

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

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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

<table>
<thead>
<tr>
<th>Status</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>Non-carriers</td>
<td>36%</td>
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<tr>
<td>BRCA1</td>
<td>44%</td>
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<tr>
<td>BRCA2</td>
<td>52%</td>
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</tbody>
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Average time for ascertainment - 9 months post diagnosis and under active follow-up for 50 months
Kaplan-Meier Cumulative Survival by *BRCA* Mutation Status

Survival, %

Years from Diagnosis

- BRCA1/2 Negative = 37%
- BRCA1 Positive = 48%
- BRCA2 Positive = 55%
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

<table>
<thead>
<tr>
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<th>Unadjusted</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P-value</td>
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<td>HR</td>
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<tr>
<td><strong>BRCA1 vs Non-Carriers (ref)</strong></td>
<td>0.51(0.34-0.76)</td>
<td>0.57(0.37-0.86)</td>
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<tr>
<td><strong>BRCA2 vs Non-Carriers (ref)</strong></td>
<td>0.35(0.18-0.65)</td>
<td>0.43(0.23-0.81)</td>
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<td></td>
<td>0.001</td>
<td>0.007</td>
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<td>0.001</td>
<td>0.009</td>
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</table>
Adjusted Cox Regression by Mutation Location and not Class I/II

BRCA1

\[ P_{\text{trend}} = 0.002 \]

BRCA2

\[ P_{\text{trend}} = 0.03 \]

BCIC Criteria
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