(Breast) Cancer Phenotype Classification by using Network based Omics Data Analysis

Sun Kim

Department of Computer Science and Engineering
Bioinformatics Institute
Interdisciplinary Program in Bioinformatics
Seoul National University
Outline

• Breast cancer and phenotypes
• Breast cancer prognosis
  – by PPI based pathway decomposition
• Breast cancer subtype classification
  – by gene regulatory network projection of pathways.
• Challenges
  – breast cancer grades and stages
• Discussion
Breast Cancer
Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2011

*For 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.


©2015, American Cancer Society, Inc., Surveillance Research

www.cancer.gov

Mutational statistics

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Predicted somatic non-silent mutations</th>
<th>Truncation mutation</th>
<th>Missense mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PKCγA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP2K1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP3K4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GATA3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MLL3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>COX1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PKB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AKT1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RHEX1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSN5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TRB3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MOBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTCF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RBB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARF2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MIF1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NF1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTEN2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRAD1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>36% 37% 8% 4% 11% 7% 7% 3% 3% 2% 4% 2% 3% 3% 3% 3% 2% 3% 2% 1% 2% 3% 3% 3% 3% 1% 2% 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal A</td>
<td>45% 12% 13% 7% 14% 8% 9% 4% 0.4% 4% 5% 2% 3% 3% 5% 4% 2% 3% 3% 1% 0.4% 1% 2% 0.4% 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>29% 29% 5% 2% 15% 8% 5% 4% 2% 2% 2% 2% 2% 4% 2% 2% 0% 0% 2% 2% 0% 5% 0% 5% 0% 5% 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>39% 72% 4% 2% 2% 7% 5% 2% 4% 2% 4% 2% 0% 0% 2% 2% 4% 2% 0% 0% 5% 0% 5% 0% 5% 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td>9% 80% 0% 0% 2% 5% 0% 1% 0% 0% 0% 0% 1% 2% 1% 0% 1% 2% 0% 1% 4% 4% 2% 0% 0% 1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages of cases with mutation by expression subtype

Risk factors

Modifiables
- Alcohol consumption
- Oral contraceptives
- Obesity
- Long-term smoking
- Tissue density
- Type 2 diabetes
- High-dose radiation

Non-Modifiables

Breast Cancer

Treatments

• Early detection is critical.
• Mammography results in 10% of false-positives.
• Therapies
  1. Radiation
  2. Chemo (before & after surgery)
  3. Hormone
     • selective estrogen receptor modifiers (= agonists & antagonists)
     • aromatase inhibitors (= inhibition of estrogen production)
     • ovarian ablation (= removal of ovary)
  4. Targeted (for HER2-enriched patients)

## Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion</th>
<th>Status</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>61%</td>
<td>NO spread to lymph node, nearby structures, outside breast</td>
<td>99%</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td>Breast tissue or lymph nodes</td>
<td>85%</td>
</tr>
<tr>
<td>Distant</td>
<td></td>
<td>lymph nodes around the collarbone or to distant lymph nodes or organs</td>
<td>25%</td>
</tr>
</tbody>
</table>

### Combined

<table>
<thead>
<tr>
<th>Survival</th>
<th>5-year</th>
<th>10-year</th>
<th>15-year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89%</td>
<td>83%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Molecular Signatures of Breast Cancer

• Will help understanding biological mechanisms underlying breast cancer.

• Can be useful for
  – Assessing risk factors,
  – Predicting patient survival, and
  – Determining treatment plans.
Breast Cancer Phenotypes
Breast Cancer Phenotype Classification

• Patient survival
  – Many successful stories
• Tumor subtypes, Metastasis
  – Also many successful
• Tumor grades
• Tumor stages
Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark
70-gene MammaPrint

• “ER-positive” and “ER-negative early stage node-negative”
• **Prediction Analysis of Microarray by 50-gene classifier**
• PAM: Nearest shrunken centroid method (PNAS, 2002)
  - simple modification of the nearest-centroid method
  - “de-noised” version of the centroids as prototypes for each class
  - amount of shrinkage determined by cross-validation
  - **Output**: minimal subset of genes that succinctly characterize each cluster

**PAM50 subtype predictor gene set**

- **1906 intrinsic genes**
  - qRT-PCR w/ FFPE performance criteria
    
    (Mullines, Clin. Chem., 2007)
    
    (= RNA data quality assessment)

- **161 genes**
  - Top “N” t-test (Methods Mol. Biol., 2003) + CV
    
    (= minimized gene set generation)

- **50 genes**
  - Centroid generation by PAM

**Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes**

Joel S. Parker, Michael Mullins, Maggie C.U. Choong, Samuel Leung, David Yodice, Takeshi Vickers, Sherri Davies, Christiane Fueron, Xiaoming He, Zhiyaan Hu, John F. Quackenbush, Inge J. Stillement, Joan Paulezzi, J.S. Marron, Andrew B. Nobel, Elaine Mardis, Torsten O. Nielsen, Matthew J. Ellis, Charles M. Perou, and Philip S. Bernard
Multi-omics subtype classification

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Comprehensive molecular portraits of human breast tumours

Methylome sequencing in triple-negative breast cancer reveals distinct methylation clusters with prognostic value
Context based Classification?

• From
  – Statistically significant gene set

• To
  – Gene selection guided by contextual information such as pathways and networks.
Network, Pathway Based Classification


Is Pathway (Context) Informative?

- *(Cancer cell, 2003)* A cell needs to overcome a number of failsafe mechanisms in order to become cancerous (Hahn and Weinberg, 2002). The cell must *evoke apoptosis and senescence programs* to survive the withdrawal of the proper growth factors and nutrients (Schmitt, 2003); it must *override DNA damage checkpoints* and *continue proliferating* to propagate existing mutations and acquire new mutations (Malumbres and Barbacid, 2001); and it must *maintain a high growth rate* to keep up with the demands of rapid cell division (Ruggero and Pandolfi, 2003).
Gene Set vs. Pathways

• It is true that selecting statistically significant gene sets without context can distinguish breast cancer subtypes quite well.
  – eg., PAM 50, Oncotype DX

• However, characterizing cancer phenotypes using pathways is desirable since pathways can help explain mechanisms underlying cancer.

• Challenge:
  – Pathway is often too big and consists of a number of functional units, not one.
Our Pathway Decomposition Strategy

Pathways → Decomposed or Projected Pathways → Classification or Prediction

Phenotype 1  Phenotype 2  . . . . . . .  Phenotype n
PPI based pathway decomposition for patient survival prediction
Motivation:
Pathway Is Too Big To Be Used for Prediction or Subtype

**Motivation:** Pathway is too big to be used for prediction or subtype.
Overview of PPI-based Pathway Decomposition

a) Transcriptome data (n = 999) and Spearman’s Correlation lead to the Breast Cancer PPI Network. MCL is used to decompose the network. KEGG and GSEA are applied to identify significant modules.

b) DP-modules for each patient are scored, and the cohort DP-module score matrix is generated. RPART is used to identify significant DP-modules for survival analysis. KM Plot is used to visualize the survival analysis results.
Decomposed Pathway and Its Activity Measurement Using RNA-seq Data

1. Decomposed Pathway (DP) identification by “Clustering of PPI Network”

2. Personalized DP Topological Activity measurement
Decomposed Pathway
(Cell Cycle example)

1. Decomposed Pathway (DP) identification by “Clustering of PPI Network”

<table>
<thead>
<tr>
<th>KEGG Pathway</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell cycle</td>
<td>34.67</td>
</tr>
<tr>
<td>Ribosome biogenesis in eukaryotes</td>
<td>29.27</td>
</tr>
<tr>
<td>DNA replication</td>
<td>24.89</td>
</tr>
<tr>
<td>Fanconi anemia pathway</td>
<td>20.54</td>
</tr>
<tr>
<td>Pyrimidine metabolism</td>
<td>17.50</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cluster</th>
<th># of genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 3</td>
<td>48</td>
</tr>
<tr>
<td>Cluster 200</td>
<td>4</td>
</tr>
</tbody>
</table>

Cluster 3 (787 genes) → GSEA → Cell cycle

Cluster 200

Cluster 3

Cell cycle
Experiment using TCGA Breast Cancer Data

- # Samples Used for Experiment
  - 999 samples (Barcode ‘tumor’ & PAM50 ‘tumor’)
- # nodes: 16,807
- # edges: 2,004,213
- MCL clusters: 1,446
- Decomposed Pathway Modules: 674
GO term (Biological Process) TCGA

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>Act</th>
<th>module value at decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>134 / 999</td>
<td></td>
</tr>
</tbody>
</table>

**Calcium ion transport (TRP)**

- TRPA1, TRPV2, TRPV3, TRPV4

Hazard ratio: 1.064
Act: 134 / 943

**(Cholesterol) sterol transport**

- ABCG5, ABCG8, APOA1, APOA4, APOB, CD36, CEL, CLPS, DGAT2, GOT2, LIPF, MOGAT2, PNLIP, SCARB1

Hazard ratio: 1.322
Act: 107 / 598

**vesicle-mediated transport**

Hazard ratio: 0.595
Act: 684.9

**Coagulation**

- TRPA1, TRPV2, TRPV3, TRPV4

Hazard ratio: 1.322
Act: 107 / 598

**Calcium ion transport (TRP)**

Hazard ratio: 1.00
Act: 134 / 999

**(Cholesterol) sterol transport**

Hazard ratio: 1.43
Act: 8.27 x 10^{-13}

**vesicle-mediated transport**

Hazard ratio: 0.53
Act: 23 / 303
How Good the DP-based Prediction?

• **Quantitative:**
  - Best scenario: 999 $\rightarrow$ 2 clusters (134+ vs. 865 –)
  - Worst scenario: 999 $\rightarrow$ 999 clusters (+, ..., +, -, ..., -)

• **Qualitative:**
  – How divergent survival lines in the KM plot?
For each patient, pathway activity is measured.

17 Clusters Chosen

Considering pathway association

17 clusters were shown to be related with Intrinsic subtypes

Comparison with Joe Navins’ Pathway based Prediction

Breast Cancer Subtype Classification
Decomposed Pathway Module based Subtype Classification
Breast Cancer Subtype Classification using Pathway and Regulatory Network

• We have shown that pathway information is useful for breast cancer subtype classification.

• Now we go one step further to include regulatory network information to show that
  – Pathway based subtype classification is possible, and
  – How these predictor pathways are differentially regulated in breast cancer subtypes.
Network Construction

• Data
  – TCGA – Breast Cancer
  – Sequencing Data (1138 Samples)
    • (Basal: 234, Normal: 175, LumA: 323, LumB: 261, Her2: 145)

• Network Construction (BRCA – subtype specific)
  – TF network
    • Inferred network by NARROMI \( \rightarrow \) 1416 TFs, 20178 TGs, 1639595 Edges
    • \textit{Filtering} : \(|\text{Pearson’s correlation}| > 0.4 \rightarrow 1283 \text{ TFs}, 11425 \text{ TGs}, 85899 \text{ Edges}
    • \textit{Filtering} : TGs == DEG \( \rightarrow \) 797 TFs, 1214 TGs, 8104 Edges
  – miRNA network
    • Network from DBs (sequence based) \( \rightarrow \) 697 miRNAs, 12133 TGs, 255427 Edges
    • \textit{Filtering} : \(|\text{Pearson’s correlation}| > 0.1 \rightarrow 358 \text{ miRNAs}, 5663 \text{ TGs}, 26282 \text{ Edges}
    • \textit{Filtering} : TGs == DEG \( \rightarrow \) 296 miRNAs, 692 TGs, 3785 Edges
Finding **Differentially Expressed Network Module**

- **Input**: Network Topology, average gene expression values for each phenotypes (classes)
- **Output**: Ranks of merged TF-modules (differentially expressed)
- **Based on information theory**

DNMPACK (cont.) – Flow of the algorithm

A. Input data: Network topology & average gene expression values for each phenotypes

B. Scoring: Mutual Information values are calculated for each TF-modules

C. Merging: Merging two TF-modules if MI increases

D. Rank: Ranking Differentially expressed Network Modules
**DNMPACK (cont.) – Mutual Information of TF-module**

Attribute Vector:

- \( a_x = [(-3, A), (0, B), (2, C)] \)
- \( a_y = [(-2, A), (1, B), (4, C)] \)
- \( a_z = [(-1, A), (3, B), (5, C)] \)

L:


\( S_1 \):

- \( H(S_1) = -1 \log(1) = 0 \)
- \( H(S_2) = -\frac{2}{3} \log\frac{2}{3} = -\frac{1}{3} \log\frac{1}{3} = 0.92 \)  
- \( H(S_2) = -\frac{1}{3} \log\frac{1}{3} = -\frac{2}{3} \log\frac{2}{3} = 0.92 \)

\( i_1 = 3 \quad i_2 = 6 \)

\( H(L) = \left( \frac{3 \times 0 + 3 \times 0.92 + 3 \times 0.92}{3 + 3 + 3} \right) = 0.61 \)
## Result

### Regulated pathways by Top-10 (TF/miRNA) module

<table>
<thead>
<tr>
<th>rank</th>
<th>ratio</th>
<th>gene count (Targeted / Total)</th>
<th>Pathway Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.39</td>
<td>14 / 36</td>
<td>DNA replication</td>
</tr>
<tr>
<td>2</td>
<td>0.31</td>
<td>39 / 124</td>
<td>Cell cycle</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>24 / 110</td>
<td>Oocyte meiosis</td>
</tr>
<tr>
<td>4</td>
<td>0.19</td>
<td>13 / 68</td>
<td>p53 signaling pathway</td>
</tr>
<tr>
<td>5</td>
<td>0.19</td>
<td>16 / 86</td>
<td>Progesterone-mediated oocyte maturation</td>
</tr>
<tr>
<td>6</td>
<td>0.14</td>
<td>12 / 86</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>7</td>
<td>0.11</td>
<td>10 / 89</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>8</td>
<td>0.08</td>
<td>12 / 146</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>9</td>
<td>0.08</td>
<td>21 / 260</td>
<td>HTLV-I infection</td>
</tr>
<tr>
<td>10</td>
<td>0.08</td>
<td>16 / 206</td>
<td>Viral carcinogenesis</td>
</tr>
<tr>
<td>11</td>
<td>0.07</td>
<td>21 / 296</td>
<td>MicroRNAs in cancer</td>
</tr>
<tr>
<td>12</td>
<td>0.06</td>
<td>11 / 171</td>
<td>Purine metabolism</td>
</tr>
<tr>
<td>13</td>
<td>0.06</td>
<td>20 / 327</td>
<td>Pathways in cancer</td>
</tr>
<tr>
<td>14</td>
<td>0.05</td>
<td>10 / 203</td>
<td>Epstein-Barr virus infection</td>
</tr>
<tr>
<td>15</td>
<td>0.05</td>
<td>11 / 225</td>
<td>Proteoglycans in cancer</td>
</tr>
<tr>
<td>16</td>
<td>0.03</td>
<td>12 / 346</td>
<td>PI3K-Akt signaling pathway</td>
</tr>
<tr>
<td>17</td>
<td>0.03</td>
<td>33 / 1179</td>
<td>Metabolic pathways</td>
</tr>
</tbody>
</table>

### Subtype classification (10-fold cross-validation)

<table>
<thead>
<tr>
<th>Features (Pathway)</th>
<th>gene count</th>
<th>Pam50 count</th>
<th>SMO</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>rank 1</td>
<td>14</td>
<td>0</td>
<td>55.0%</td>
<td>61.2%</td>
</tr>
<tr>
<td>rank 1~2</td>
<td>46</td>
<td>4</td>
<td>71.2%</td>
<td>69.9%</td>
</tr>
<tr>
<td>rank 1~3</td>
<td>55</td>
<td>4</td>
<td>72.8%</td>
<td>74.1%</td>
</tr>
<tr>
<td>rank 1~4</td>
<td>58</td>
<td>5</td>
<td>73.4%</td>
<td>73.6%</td>
</tr>
<tr>
<td>rank 1~5</td>
<td>58</td>
<td>5</td>
<td>73.4%</td>
<td>73.6%</td>
</tr>
<tr>
<td>rank 1~6</td>
<td>61</td>
<td>6</td>
<td>73.8%</td>
<td>74.8%</td>
</tr>
<tr>
<td>rank 1~7</td>
<td>62</td>
<td>6</td>
<td>73.7%</td>
<td>74.1%</td>
</tr>
<tr>
<td>rank 1~8</td>
<td>63</td>
<td>7</td>
<td>73.8%</td>
<td>73.7%</td>
</tr>
<tr>
<td>rank 1~9</td>
<td>69</td>
<td>8</td>
<td>74.6%</td>
<td>76.3%</td>
</tr>
<tr>
<td>rank 1~10</td>
<td>72</td>
<td>8</td>
<td>75.1%</td>
<td>77.2%</td>
</tr>
<tr>
<td>rank 1~11</td>
<td>82</td>
<td>8</td>
<td>76.6%</td>
<td>78.6%</td>
</tr>
<tr>
<td>rank 1~12</td>
<td>89</td>
<td>8</td>
<td>77.9%</td>
<td>78.1%</td>
</tr>
<tr>
<td>rank 1~13</td>
<td>94</td>
<td>8</td>
<td>77.7%</td>
<td>78.0%</td>
</tr>
<tr>
<td>rank 1~14</td>
<td>95</td>
<td>8</td>
<td>77.3%</td>
<td>78.1%</td>
</tr>
<tr>
<td>rank 1~15</td>
<td>100</td>
<td>9</td>
<td>78.7%</td>
<td>80.1%</td>
</tr>
<tr>
<td>rank 1~16</td>
<td>102</td>
<td>9</td>
<td>79.2%</td>
<td>79.6%</td>
</tr>
<tr>
<td>rank 1~17</td>
<td>128</td>
<td>10</td>
<td>79.7%</td>
<td>80.1%</td>
</tr>
</tbody>
</table>
Luminal B

hsa-mir-30a → MYBL2

hsa-mir-149 → 3.30

hsa-let-7b → 0.89

MYBL2 → 1.78

SKP2 → 0.32

TF #1 → 0.32

TF #2 → 0.13

TF #1

TF #2

MYBL2

SKP2

TF #1

TF #2
**Her2**

- **hsa-mir-30a**: 0.47
- **hsa-mir-149**: 2.62
- **hsa-let-7b**: 0.65

**MYBL2**
- **SKP2**: 1.97
- **TF #1**: 0.44
- **TF #2**: 0.16

**TF #1**
- **TF #2**

**Cell Cycle**
- **TOP**: DNA damage checkpoint
- **ARF**: Cell cycle regulation
- **p53**: DNA damage response
- **Bcl-2**: Apoptosis regulation
- **Cyclin D1**: Cell cycle regulator
- **p21**: Cell cycle inhibitor
- **Rb**: Cell cycle regulator

**Genes and Proteins**
- **Cyclin D1**: Cell cycle regulator
- **p21**: Cell cycle inhibitor
- **Rb**: Cell cycle regulator
- **p53**: DNA damage response
- **Bcl-2**: Apoptosis regulation

**Gene Expression**
- **MYBL2**: 1.97
- **SKP2**: 0.44
- **TF #1**: 0.16
- **TF #2**: 0.35

**Disease Pathways**
- **Oncomap**: Tumor suppression pathways
- **p53**: DNA damage response
- **Bcl-2**: Apoptosis regulation

**MicroRNAs**
- **hsa-mir-30a**: 0.47
- **hsa-mir-149**: 2.62
- **hsa-let-7b**: 0.65
Grade, Stage Classification?
Cell cycle Pathway Activation in Subtypes
Cell cycle Pathway Activation in Subtypes w.r.t Average expr
Cell cycle: grade

grade1

grade2

grade3
Discussion

• We showed that pathways are very informative for breast phenotype classification, but only when decomposed or projected to smaller units.

• Breast cancer grades and stages?
• Combining subtype and survival classification?
• How much predictive power gained when epigenetic information is added?
Lab Members (2015 Day1)
Research Funding

• Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP(NRF-2014M3C9A3063541)
• BIT Education (NRF Korea-2012M3A9D1054622).
• Next-Generation Information Computing Development Program (NRF Korea -2012M3C4A7033341).
• US National Cancer Institute, Integrated Cancer Biology Program, Center for Cancer Systems Biology, funded by [U54 CA113001] (Interrogating Epigenetic Changes in Cancer Genomes)
Thank you!