

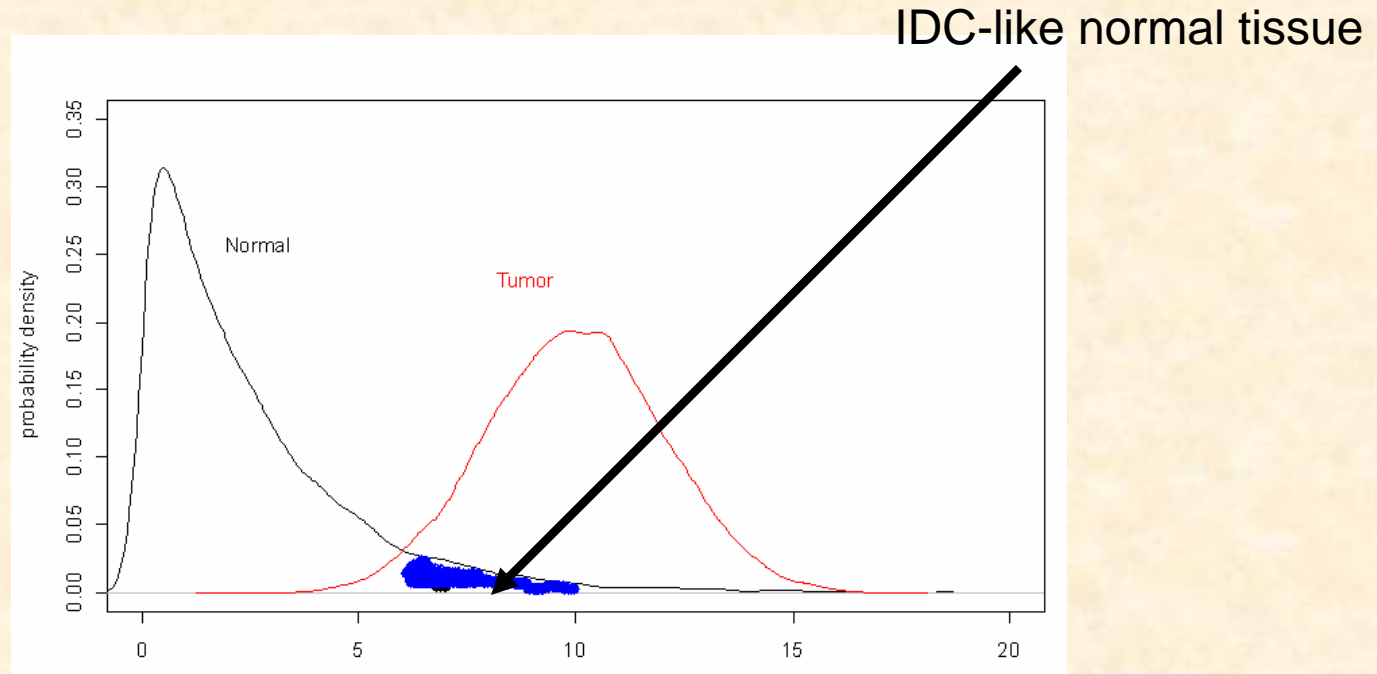
Supplementary Figure 1:

A Heuristic Algorithm of IDC-like Normal Tissue Approach

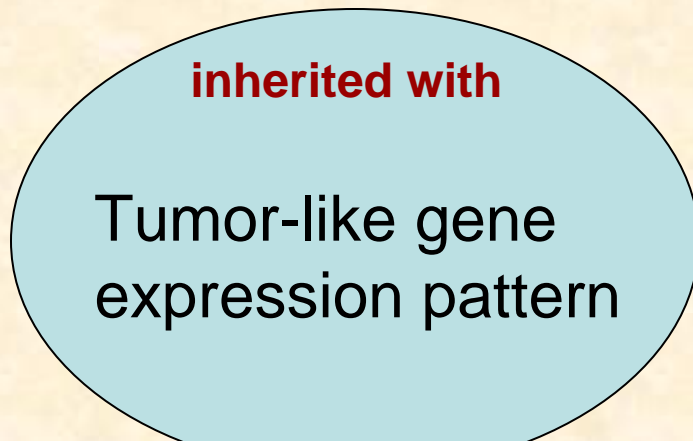
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Hypothesis of IDC-like Normal Tissue



Histological-normal tissue → Cancer development



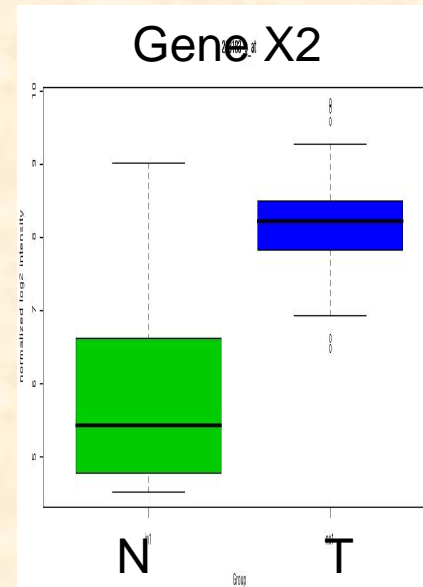
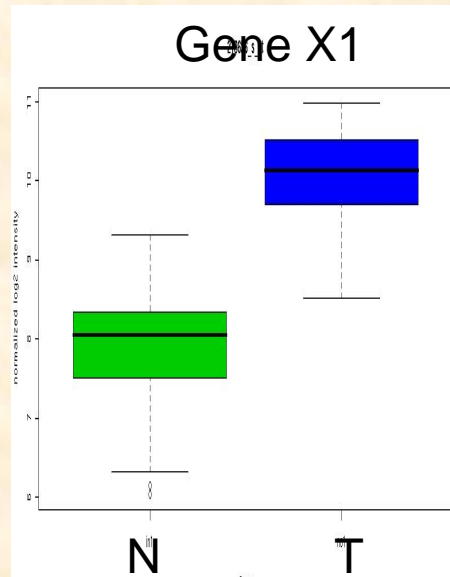
→ High-risk genes

Hypothesis of IDC-like Normal Tissue (Cont.)

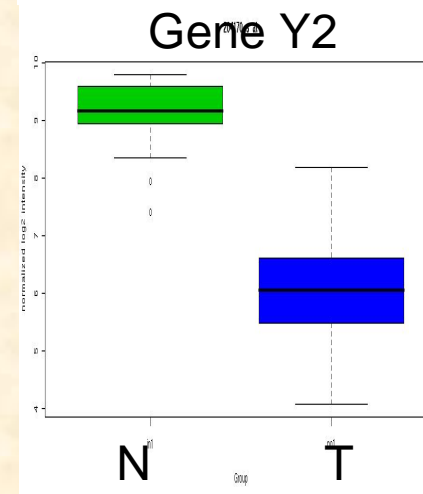
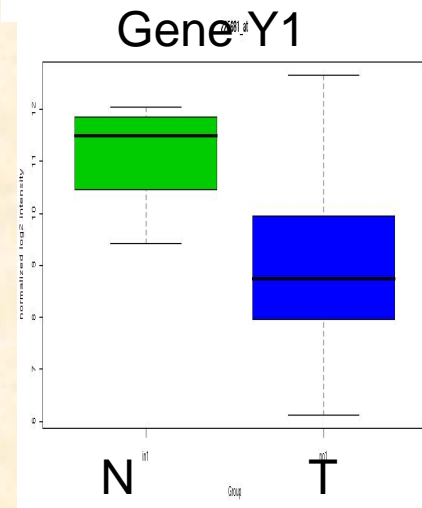
- **Definition** of IDC-like normal tissue: breast normal tissue classified as normal in histological level, but abnormal in molecular level.
- **Assumption:**
 - The IDC-like normal tissue has tumor-like gene expression. That is, expression of tumor genes (differentiate tumor from normal) in IDC-like normal tissue is similar to or close to the one in tumor tissue.
 - Thus, an IDC-like normal tissue is likely to have higher expression (up or down) of tumor genes compared to the rest of normal tissues.
 - As a result, its rank (among all normal tissues) tends to be high in the majority of up-regulated tumor genes. Or, its rank tends to be low in the majority of down-regulated tumor genes.

Step 1: Identify Tumor Genes

Up-
Regulation



Down-
Regulation

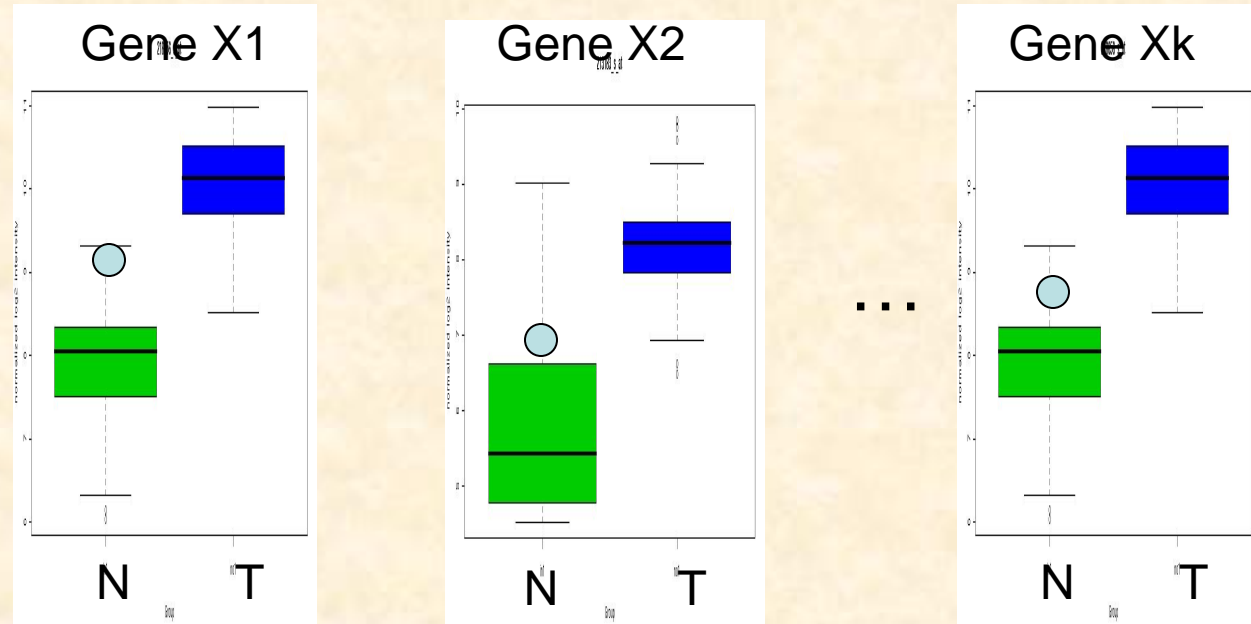


Step 2: Identify IDC-like Normal Tissues

For each normal tissue (say Tissue A):

Step 2.1: Collect rank percentiles of tissue A in all up-regulated genes.

Up-Regulated
Genes

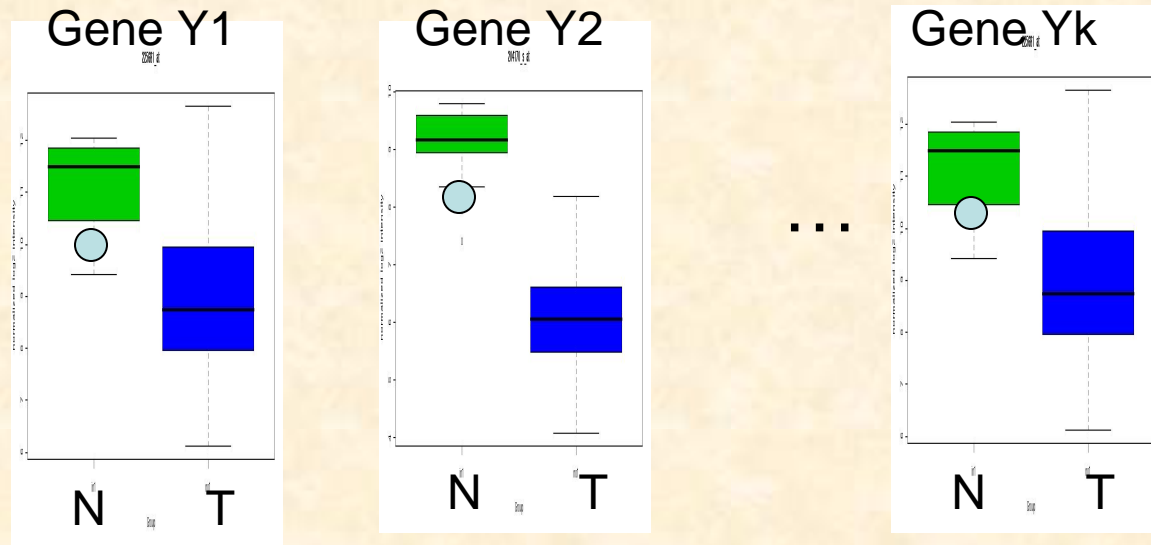


Collect rank percentiles: 0.98, 0.78, 0.85,...

Step 2.2: Collect rank percentiles of tissue A in all down-regulated genes.

Normal Tissue A:

Down-Regulated Genes



Collect rank percentiles: 0.12, 0.02, 0.23,...

Step 2.3: Examine distribution of rank percentiles of tissue A to determine to be an IDC-like normal tissue.

For an IDC-like normal tissue, the distribution is expected to be skew to the top (for up-regulated genes) or to the bottom (for down-regulated genes). For a non-IDC-like normal tissue, the distribution tends to be centered at the middle or to be skew in opposite direction (compared to IDC-like normal).

**IDC-like normal tissue
 (potential high-risk)**

Non-IDC-like normal tissue

