Gene Expression Profiling Predicts Clinical Outcome of Breast Cancer

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Source: Laura J van 't Veer, Dai, H., Marc J van, d. V., He, Y. D., & al, e. (2002). Gene expression profiling predicts clinical outcome of breast cancer. *Nature, 415*(6871), 530-6. doi:http://dx.doi.org/10.1038/415530a

What is the problem?

- Existing predictors for metastases inaccurately classify breast tumours according to their clinical behaviour
- 70-80% of patients receiving unnecessary adjuvant therapy
- Demand for patient-tailored therapy strategies

Why is this problem important?

- Patients may potentially suffer from the side effects of these treatments
- Tailored adjuvant systemic treatment could greatly reduce the cost of breast cancer treatment

How is the solution achieved?

Goal: identify a gene expression signature that can predict good or poor prognosis

1. Gene expression profiling

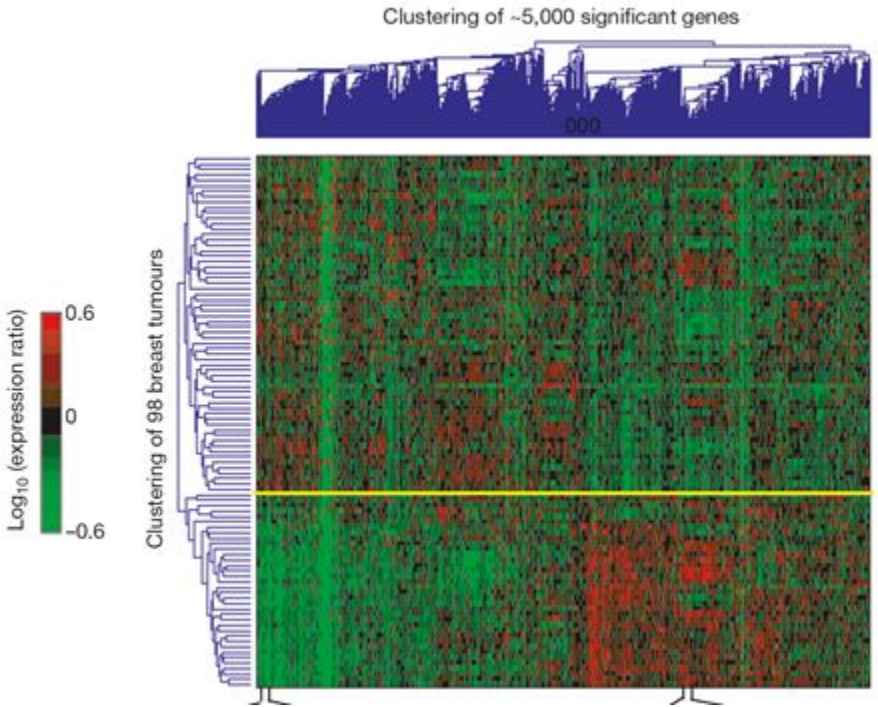
2. Unsupervised classification (two-dimensional clustering analysis)

3. Supervised classification (prognosis classifier and *BRCA1* diagnostic classifier)

Gene Expression Profiling

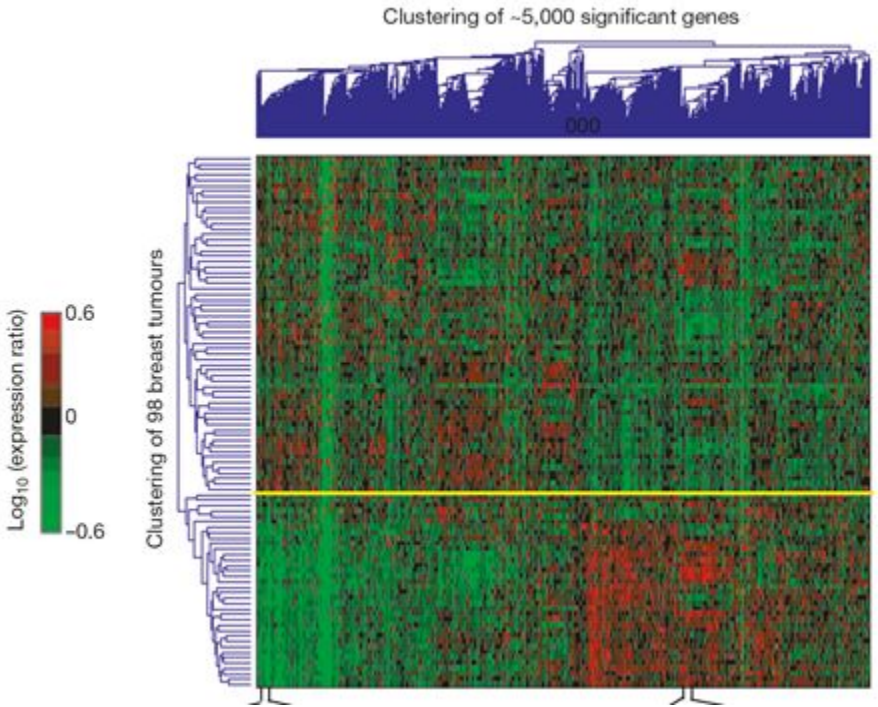
- Determined the transcript abundance of genes expressed in breast cancer tumours
- ~5000 significant genes were found to be significantly regulated across the tumour samples

Clustering Algorithm



- Categorized primary breast tumours based their similarities over these ~5000 significant genes
- Y-axis: relatedness of breast tumours
- X-axis: expression of each gene

What was found from the clustering algorithm?



- There are 2 distinct subgroups of tumours (separated by the yellow line)
- Upper group generally had “good prognosis”
- Lower group generally had “poor prognosis”

Prognosis Classifier

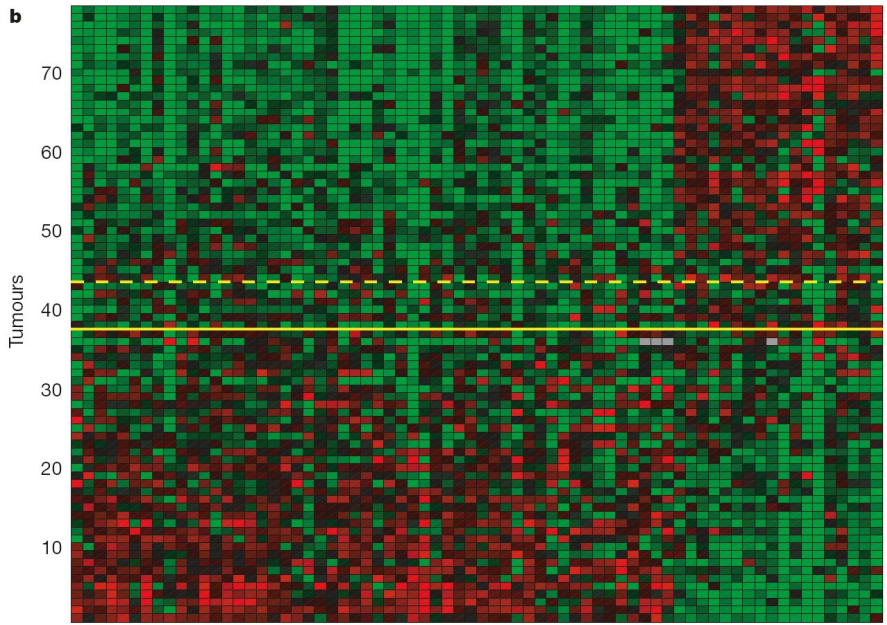
Created to reliably identify good and poor prognosis

1. ~5000 significant genes were narrowed down to 231 genes based on their correlation to disease outcome (correlation coefficient)

2. Ranked based on the magnitude of the correlation coefficient

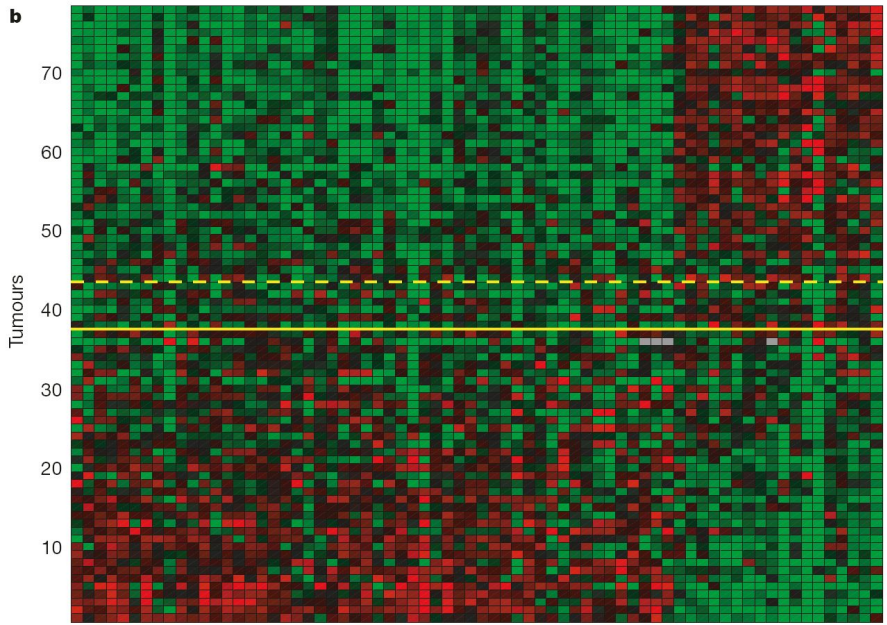
3. These genes were optimized using the “leave-one-out” method to select 70 marker genes

Prognosis Classifier



- Threshold for selecting patients for adjuvant therapy adjusted to be more sensitive (yellow dotted line)
- Reduced number of poor prognosis patients being misclassified into good prognosis group

Prognosis Classifier



- Above threshold (dotted line) = good prognosis
- Below threshold (dotted line) = poor prognosis
- Rows = tumour
- Columns = genes

How do these results compare?

Table 1 Breast cancer patients eligible for adjuvant systemic therapy

Consensus	Patient group: Total patient group ($n = 78$)	Metastatic disease at 5 yr ($n = 34$)	Disease free at 5 yr ($n = 44$)
St Gallen	64/78 (82%)	33/34 (97%)	31/44 (70%)
NIH	72/78 (92%)	32/34 (94%)	40/44 (91%)
Prognosis profile*	43/78 (55%)	31/34 (91%)	12/44 (27%) (18/44 (41%)†)

- Prognosis classifier selects high-risk patients who would benefit from adjuvant treatment just as effectively as pre-existing tools
- Significant reduction in the number of patients receiving unnecessary treatment

Key findings of the Prognosis Classifier

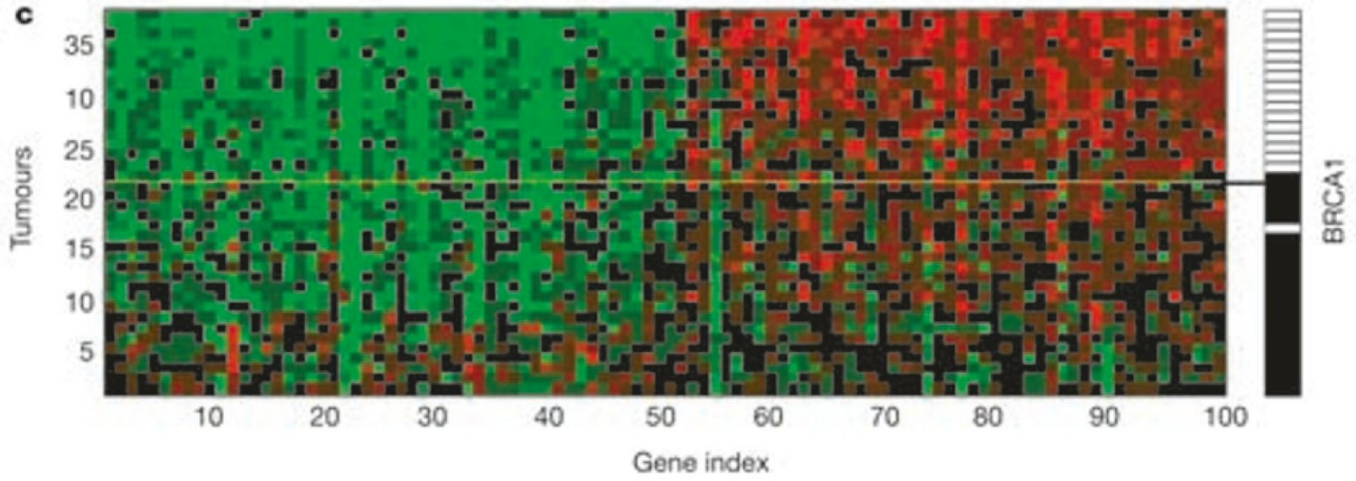
- Small primary tumours that have yet to metastasize can display a poor prognosis signature
- Genes that predict poor prognosis include genes involved in cell cycle, invasion and metastasis, angiogenesis, and signal transduction
- This prognosis classifier is a superior predictor of disease outcome than currently available tools

A Novel *BRCA1* Signature

- Clustering algorithm was previously shown to distinguish between ER-positive and ER-negative tumours
- *BRCA1*: tumour suppression gene that repairs DNA
- Mutations of the *BRCA1* gene are inherited; increased risk for breast cancer
- ER-negative breast tumours were subsequently classified into sporadic or *BRCA1* subgroups based on the expression of 100 optimal *BRCA1* reporter genes

A Novel *BRCA1* Signature

- Above the yellow line = have a *BRCA1* signature based on the expression of 100 optimal *BRCA1* reporter genes



What are some limitations of this study?

- Small sample size (n = 98, 78)
- Patients were selected based on specific criteria: age, size of primary tumour, metastases, etc.
- Need to test prognosis classifier on a large and unselected group of patients

How can gene expression profiling be used?

- Provides a powerful tool to create patient-specific treatments
- The signature that predicts prognosis can be used to determine appropriate therapy (e.g. adjuvant therapy or not)
- The signature that defines *BRCA1* status can supplement our understanding of how to improve diagnosis of hereditary breast cancer
- Genes overexpressed in tumours with a poor prognosis profile are potential targets for novel drugs