Technology meets the patient and patient meets technology:

Exploiting the human genome to improve cancer diagnostics

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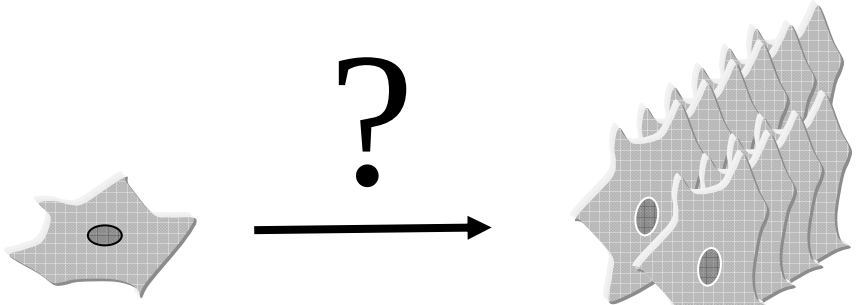
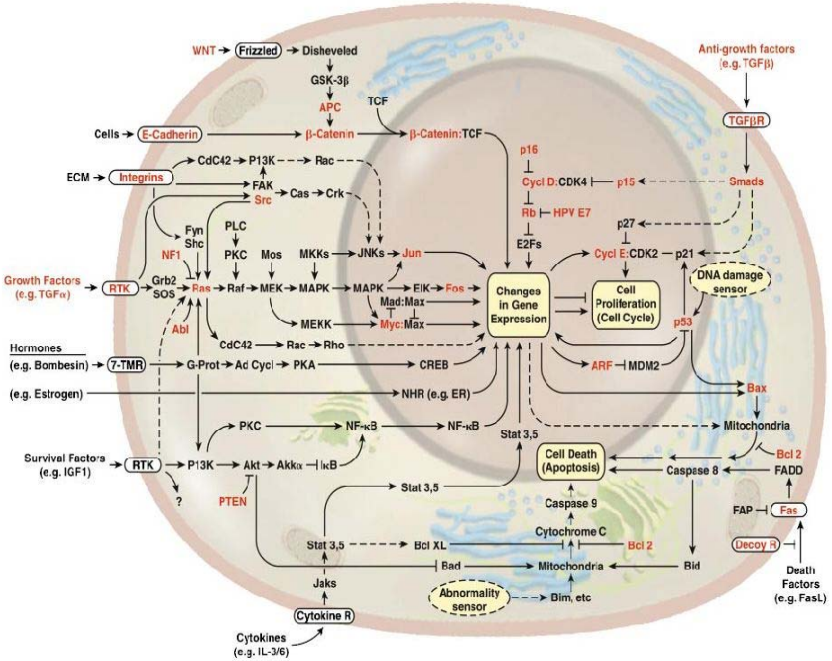
Agendia™

Over 25 years of progress in cancer research



Normal cell

Cancer



1980

2006

In spite of all this progress:

- We still use the light microscope for cancer diagnosis
- We still use many broadly-acting cytotoxic drugs to treat cancer

Genomic technologies can help up to:

- Develop better cancer diagnostics
- Develop more specific cancer therapeutics

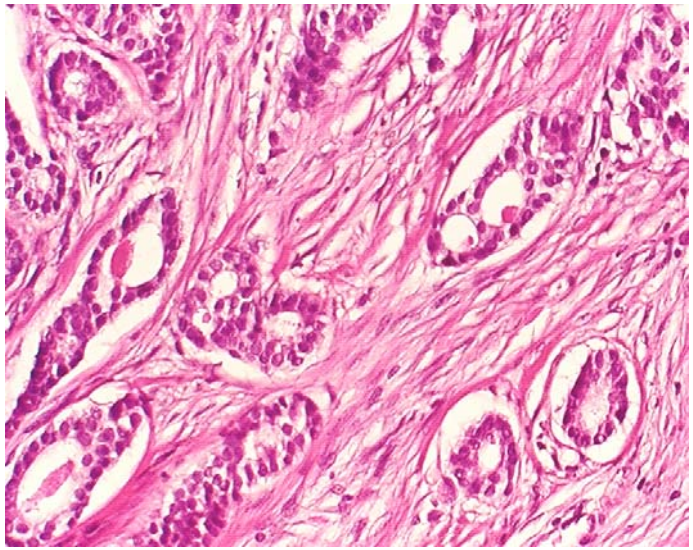
The microscope, a major tool for diagnostics for the last 350 years

Van Leeuwenhoek microscope, late 1600s

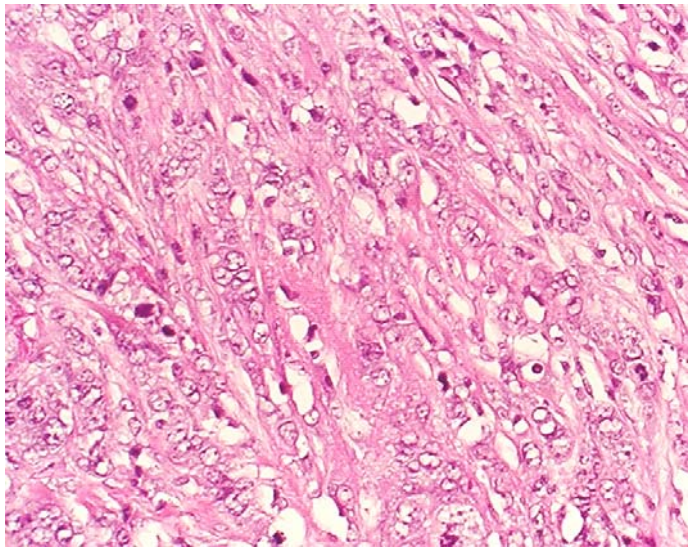
Olympus microscope, late 1900s

Using microscopy to predict disease outcome in cancer

- Grade 1



- Grade 3

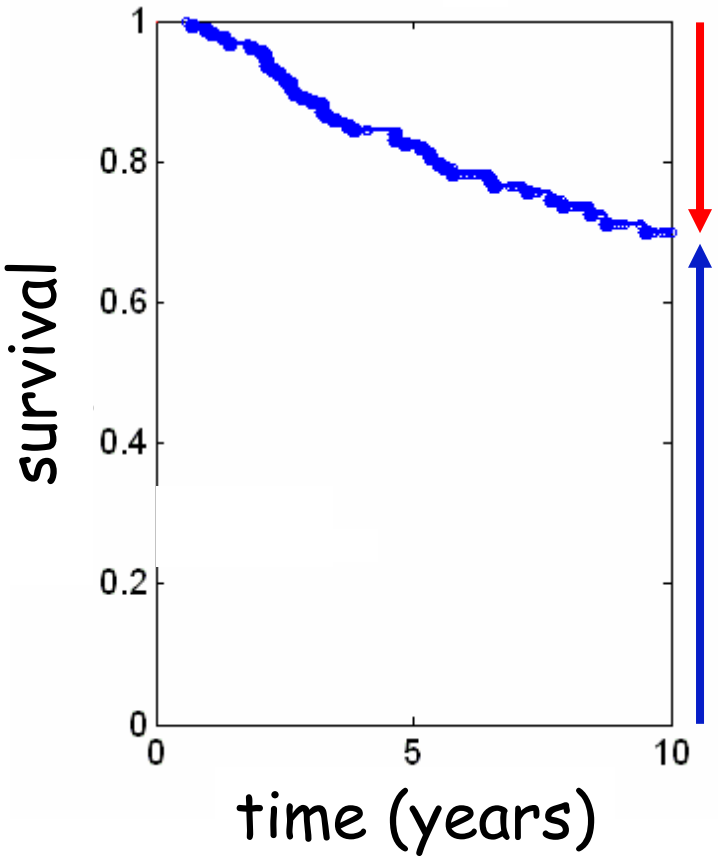


Histological grade

Breast Cancer - Survival

Pre-menopausal patients, lymph node negative

Kaplan-Meier Survival Curve



~30% die of breast cancer

~70% survive breast cancer

Breast Cancer - Treatment
premenopausal, lymph node negative

Current adjuvant treatment selection criteria:

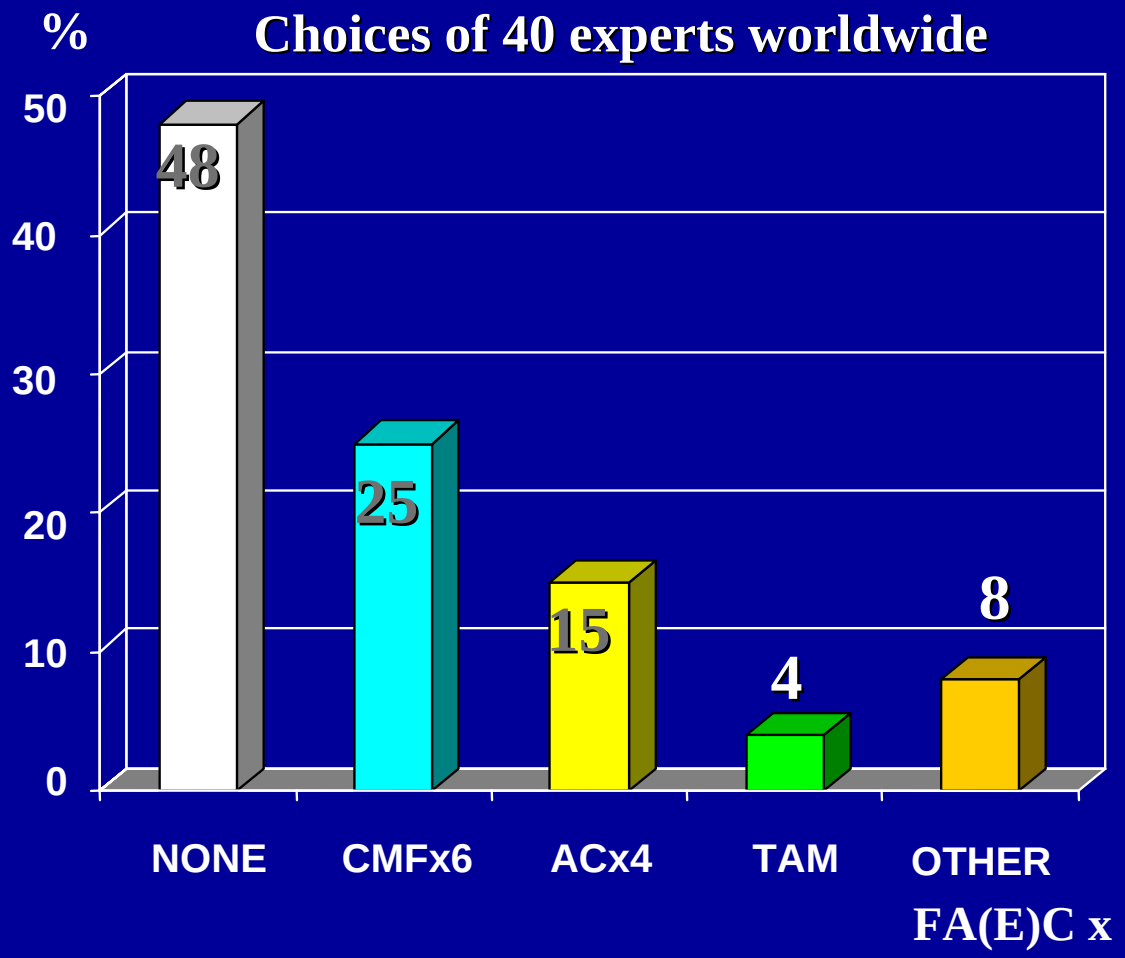
- NIH (US) consensus criteria: > 95%
- St Gallen (EU) consensus criteria: > 80%

  receive adjuvant chemo- and hormonal therapy

As only 30% of these patients develop distant metastases, some 50-65% of patients are over-treated with adjuvant (chemo)therapy

SHOULD ONE TREAT A SMALL (<1CM) ENDOCRINE UNRESPONSIVE BREAST TUMOR ?

61 y-old, fit, postmenopausal
Node negative
pT = 0.9 cm
ductal cancer
ER and PR negative
HER2 negative
Grade 2



FA(E)C x 6

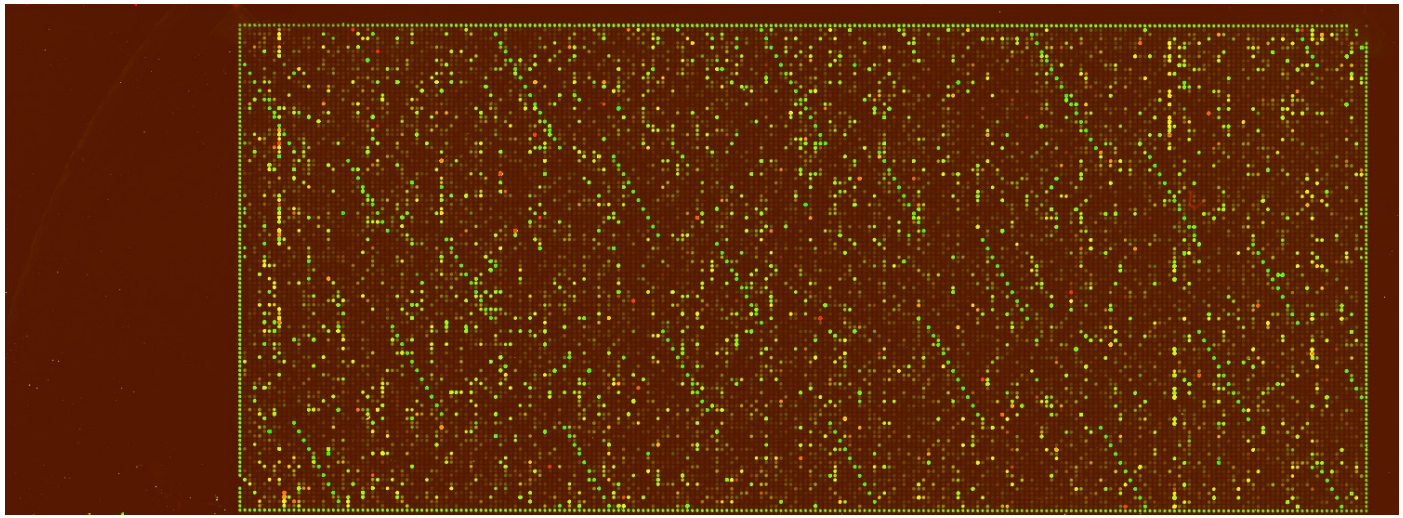
Courtesy of Martine Piccart

Few data, little information

Tumor cell behavior is determined by the activity of many genes

- The activity of one or a few genes cannot predict tumor cell behavior in a reliable way.
- We need tools to measure the activity of many genes in a single experiment

Gene Expression Profiling

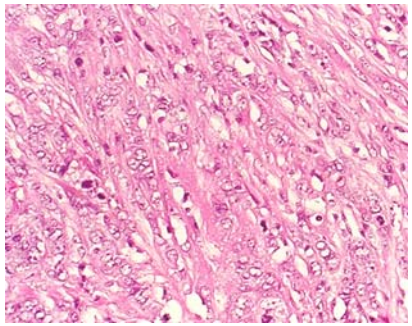


Measure the activity of tens of thousands of genes in a single experiment

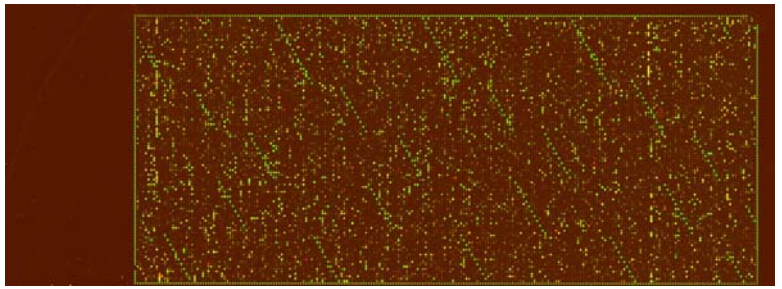
"molecular portrait of cancer"

From micro-scope to micro-array

Micro-scope

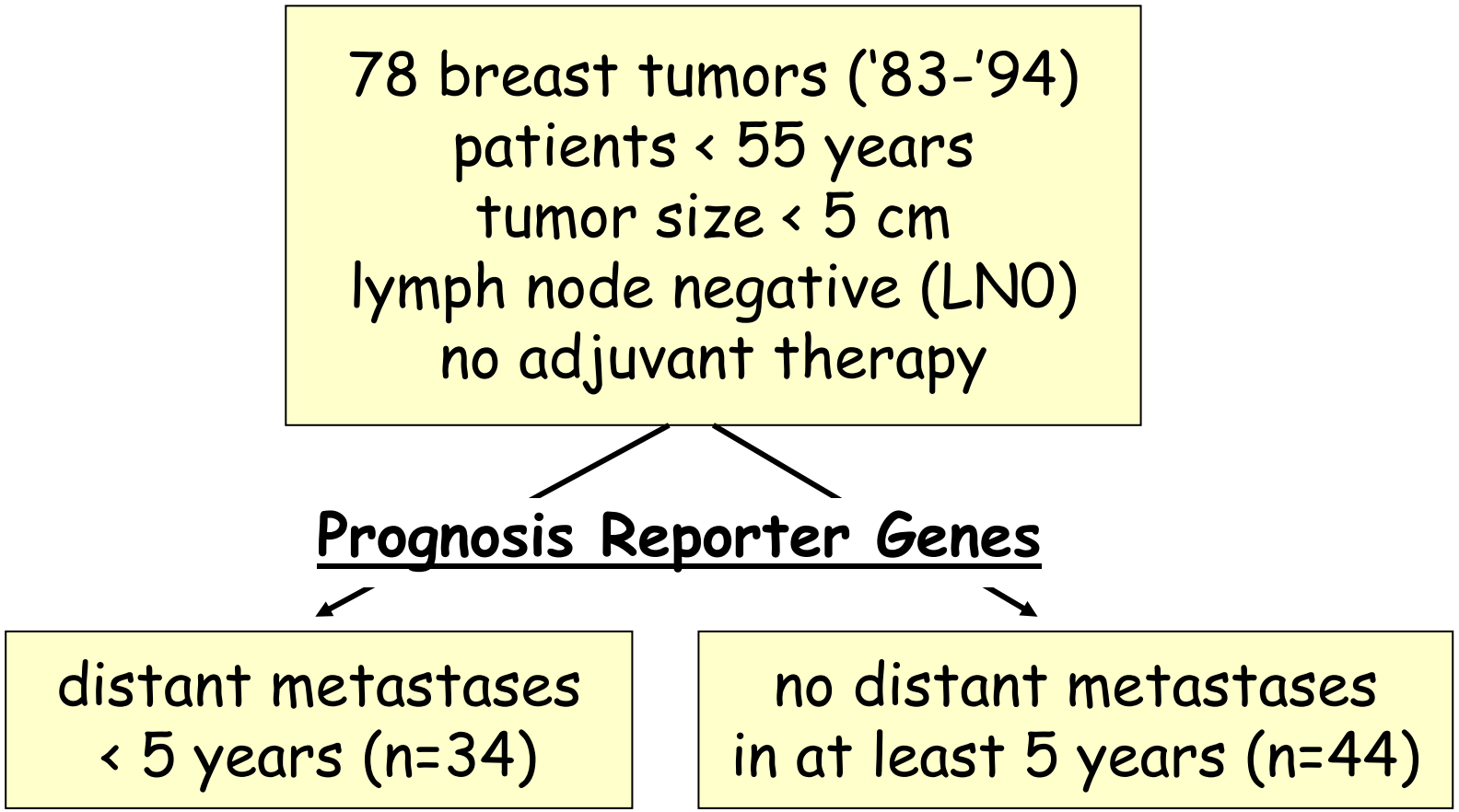


Micro-array

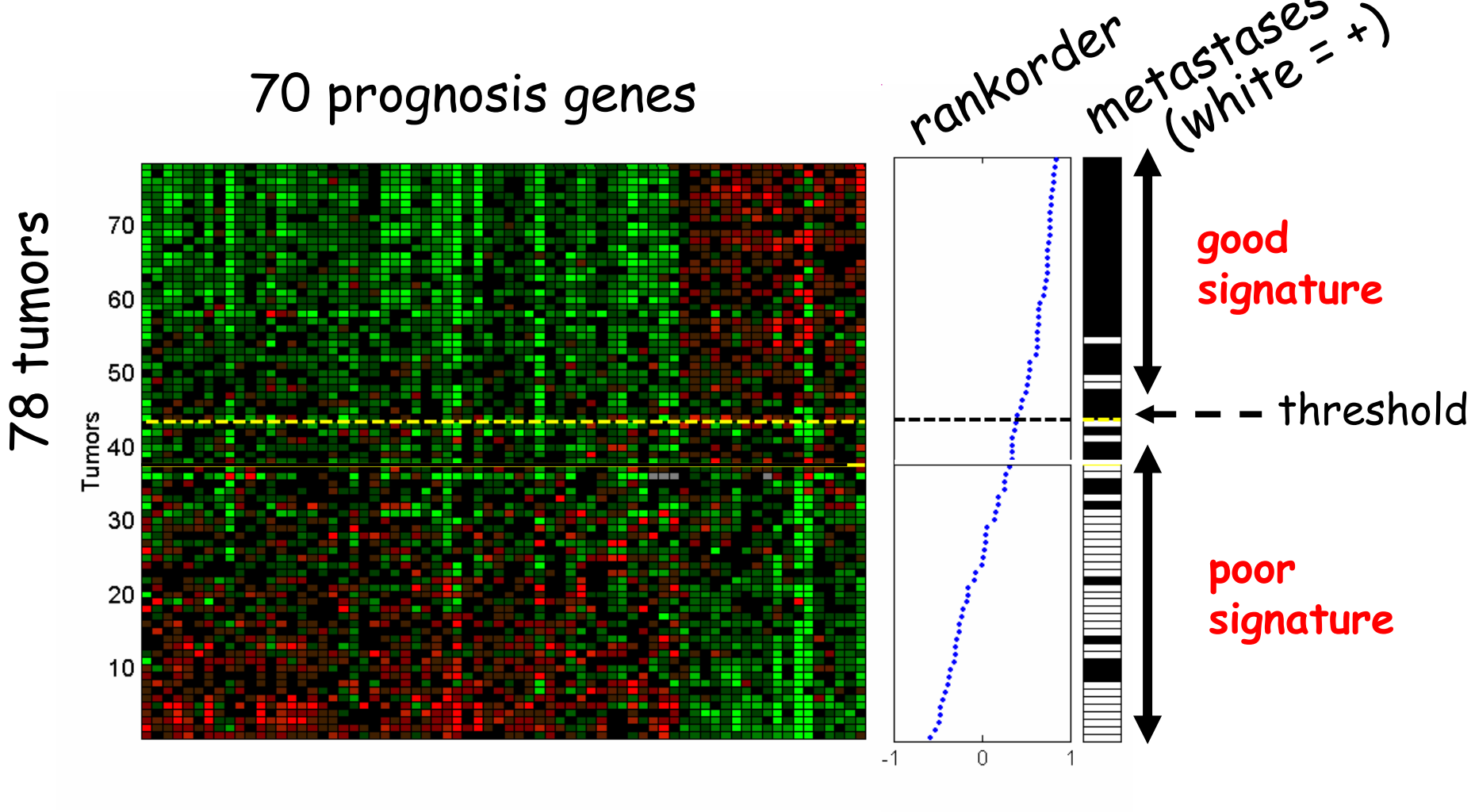


Can gene expression profiling be used to more accurately predict clinical outcome of disease in breast cancer?

Supervised Classification for prognostic subclasses



Microarray-based prognosis of breast cancer

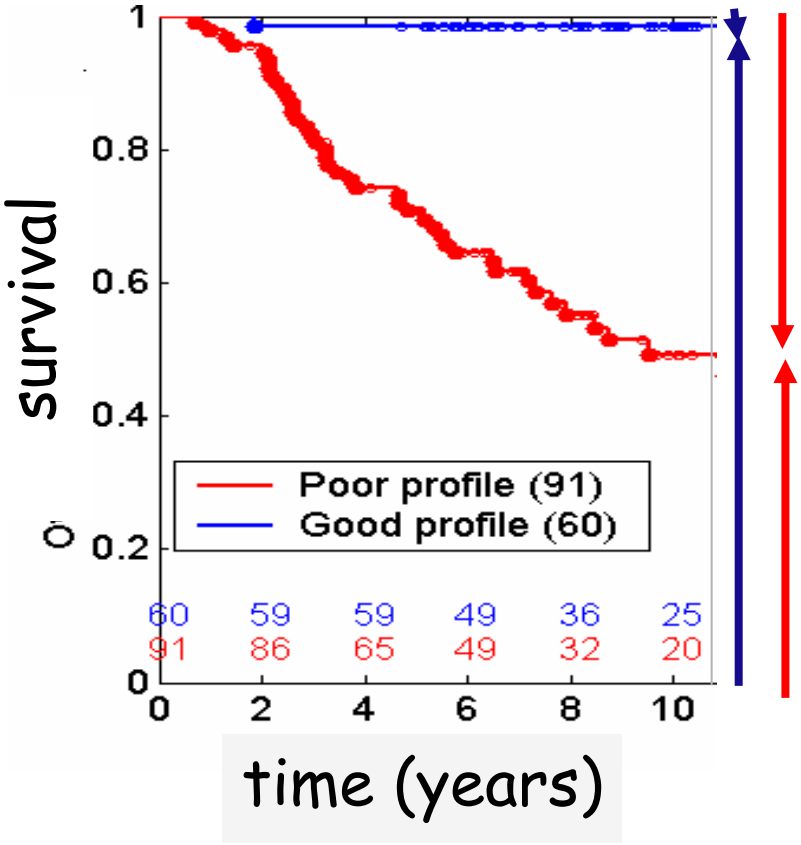


threshold set at 10% false negatives

91 % sensitivity, 73% specificity

Breast Cancer - Survival by profiling

Distinguish in: 40% good profile, 60% poor profile

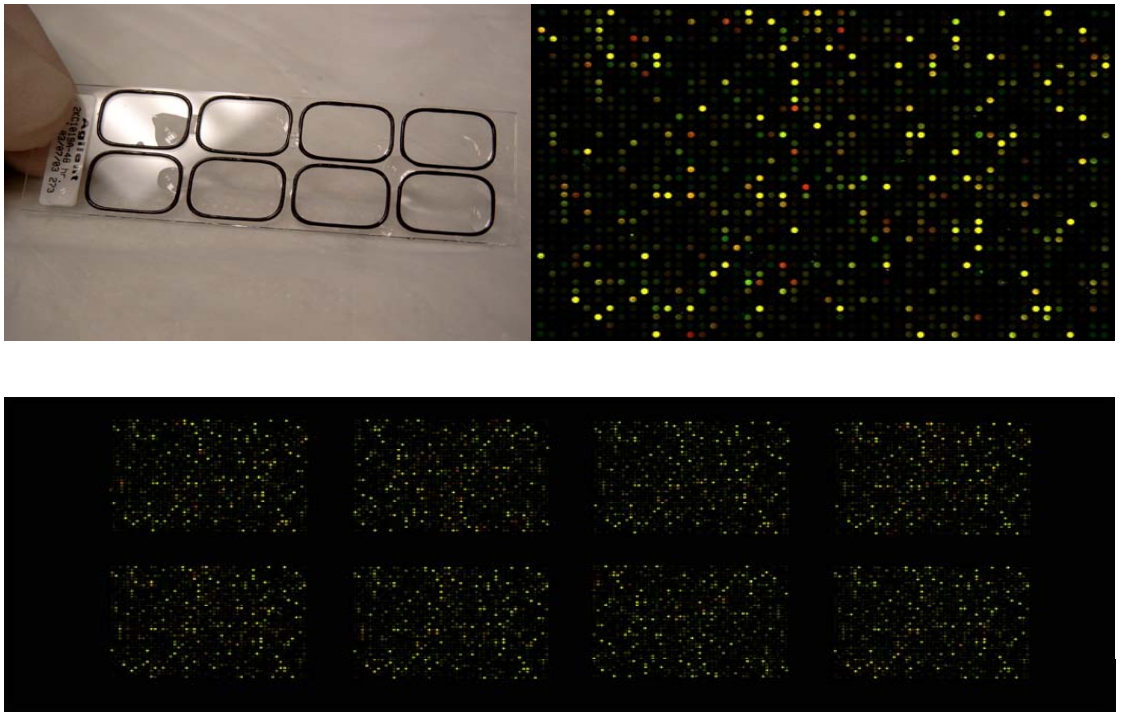


good profile:
~4% die of breast cancer
~96% survive breast cancer

poor profile:
~50% die of breast cancer
~50% survive breast cancer

151 patients, <53, LN0
10 year survival curve

"MammaPrint"
Breast cancer prognosis array



Regulatory; QA/QC:

CLIA -registered, ISO 17025-certified,

CE- marked, FDA registration ongoing

Agendia™

Changing attitudes about complex gene tests in clinical practice

2002:

Breast cancer prognosis profile identified:

Not a single diagnostic company interested to commercialize the 70-gene breast cancer prognosis test

2004:

Commercial launch MammaPrint by Agendia

"St. Gallen" breast cancer consensus meeting votes against microarray testing 34 to 0

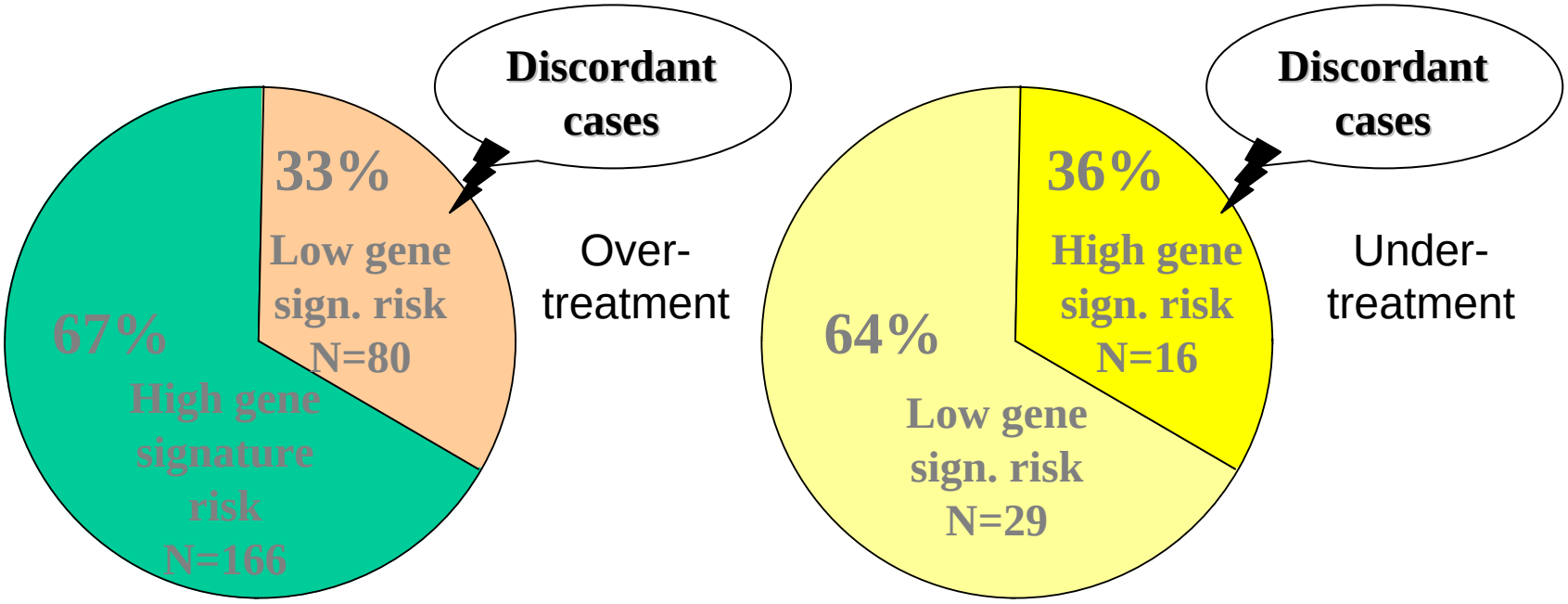
2006:

At ESMO, 50% of audience votes in favor of microarray tests for ALL patients, 90% in favor in special cases

In 2006, over 15,000 gene tests will be sold in USA for breast cancer

CONCORDANCE BETWEEN CLINICAL AND GENE SIGNATURE RISK CLASSIFICATION

Threshold for low clinical risk defined as predicted 10-year O.S. > 90%



High clinical risk N=246 **Low clinical risk N=45**

Discordant cases with other clinical risk classifications	
St-Gallen = 35% NPI = 36%	St-Gallen = 43% NPI = 54%

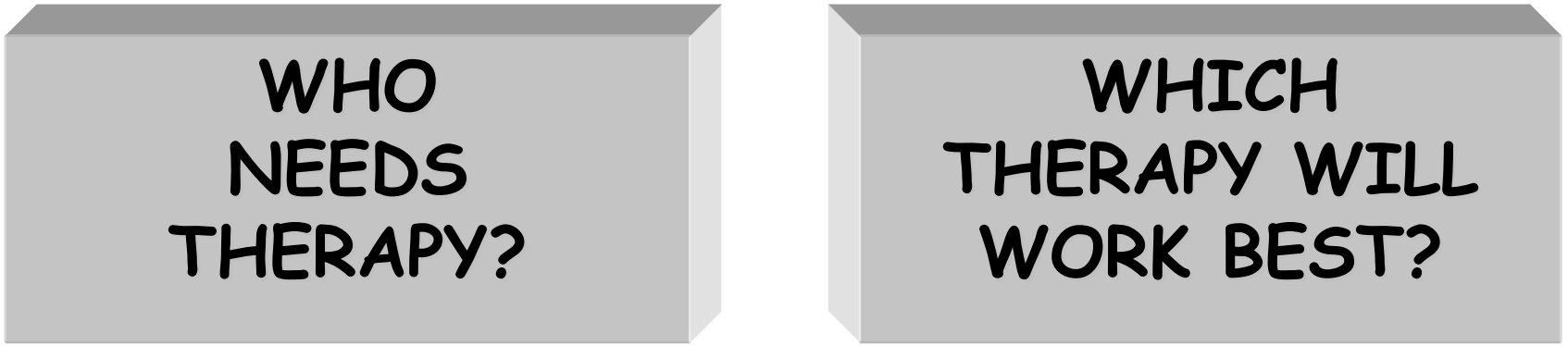
Clinical applications of microarrays

Who to treat:

- Prognosis profiles as diagnostic tool
  -> improved selection for adjuvant therapy

How to treat:

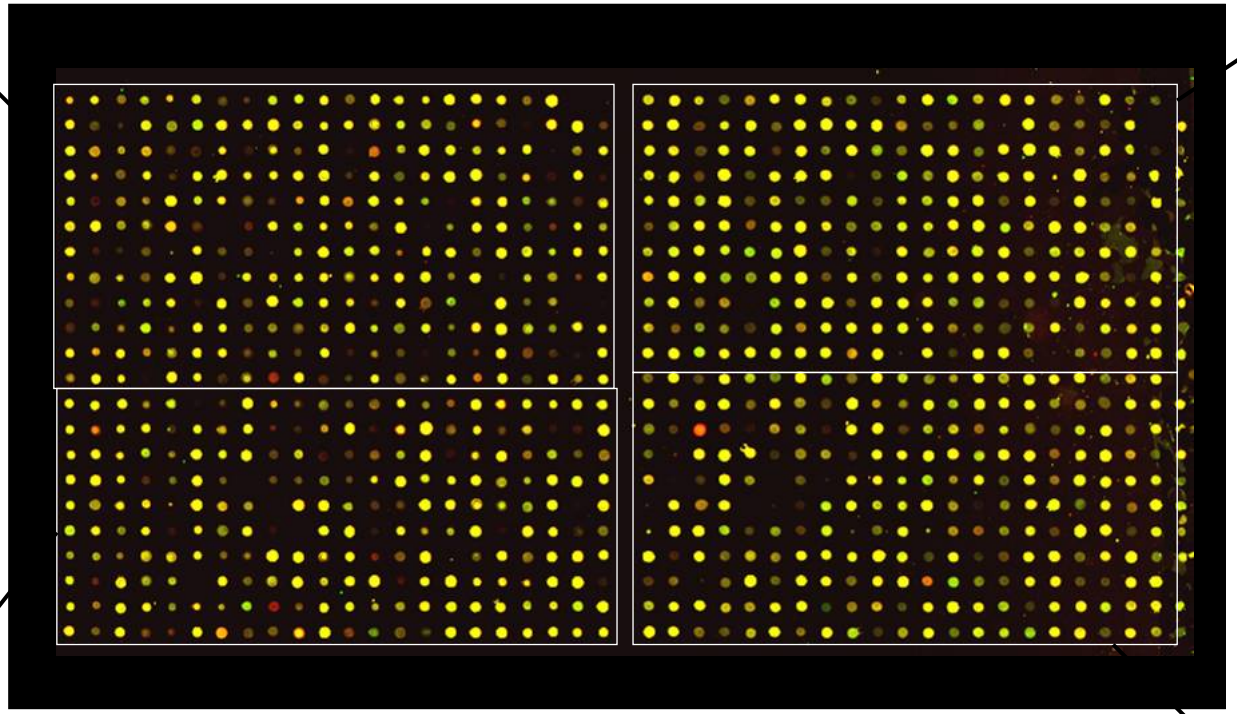
- Predictive profiles for drug response
  -> selection of patients who will benefit most



The (near) future: Multiple predictions made by a single micro-array test

Will the tumor come back?

Will the tumor respond radiation?



Will the tumor respond do drug A?

Will the tumor respond do drug B?

Acknowledgements

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