Genomic Medicine and Breast Cancer Past, Present, and Future

Stan Lipkowitz

Senior Investigator
Laboratory of Cellular and Molecular Biology, CCR
Attending Physician, MOB, NCI and Oncology, NNMC

February 3, 2012

Genomic Medicine and Breast Cancer

Genomic Medicine Definition

The use of molecular Genotype (DNA) and Phenotype (mRNA) to predict disease incidence, outcome, and/or to dictate treatment

Genomic Medicine and Breast Cancer

Genomic Medicine Definition

The use of molecular Genotype (DNA) and Phenotype (mRNA) to predict disease incidence, outcome, and/or to dictate treatment

In cancer biology there are two genomes

Tumor (somatic)

Patient (germline)

Genomic Medicine and Breast Cancer Past

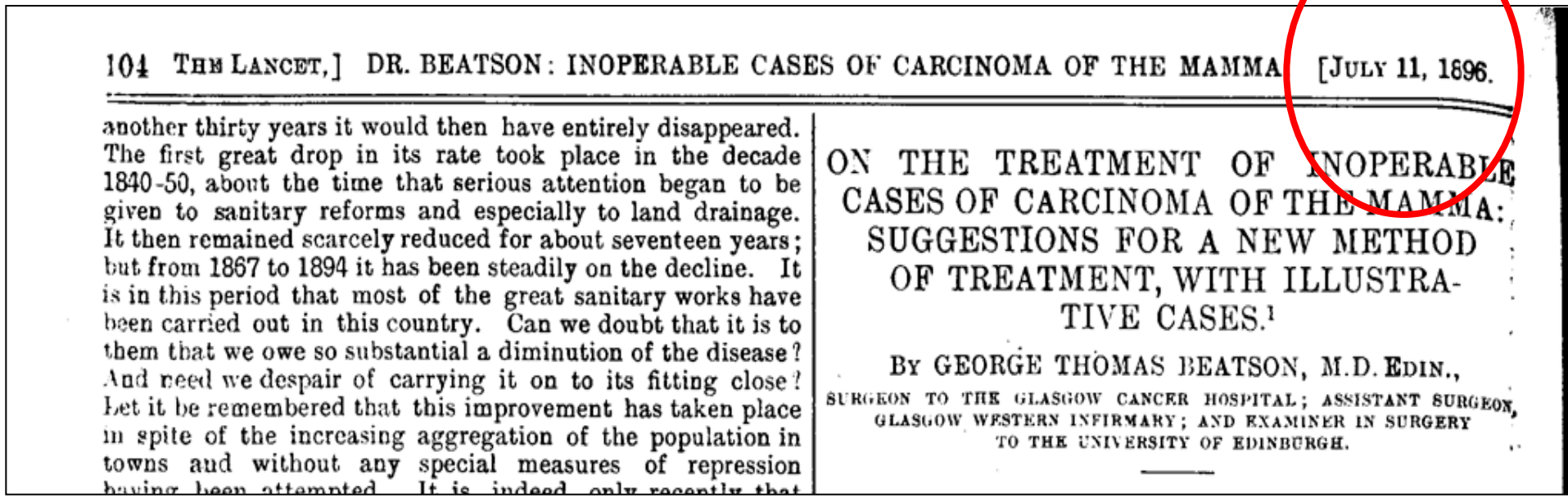
Treatment based on:

Clinical features of the tumor
(size, pathologic grade, nodal metastasis)

Expression and/or genetic abnormalities of one or a few genes in the tumor

The First Therapy Based on Tumor Phenotype

Estrogen Receptor



104 THE LANCET,] DR. BEATSON: INOPERABLE CASES OF CARCINOMA OF THE MAMMA. [JULY 11, 1896.

another thirty years it would then have entirely disappeared. The first great drop in its rate took place in the decade 1840-50, about the time that serious attention began to be given to sanitary reforms and especially to land drainage. It then remained scarcely reduced for about seventeen years; but from 1867 to 1894 it has been steadily on the decline. It is in this period that most of the great sanitary works have been carried out in this country. Can we doubt that it is to them that we owe so substantial a diminution of the disease? And need we despair of carrying it on to its fitting close? Let it be remembered that this improvement has taken place in spite of the increasing aggregation of the population in towns and without any special measures of repression having been attempted. It is indeed only recently that

ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,

SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

Beatson, Lancet 148: 104, 1896

The First Therapy Based on Tumor Phenotype

Estrogen Receptor

Case History

33 year old premenopausal woman presented with a 11 X 8 cm left breast tumor with skin involvement

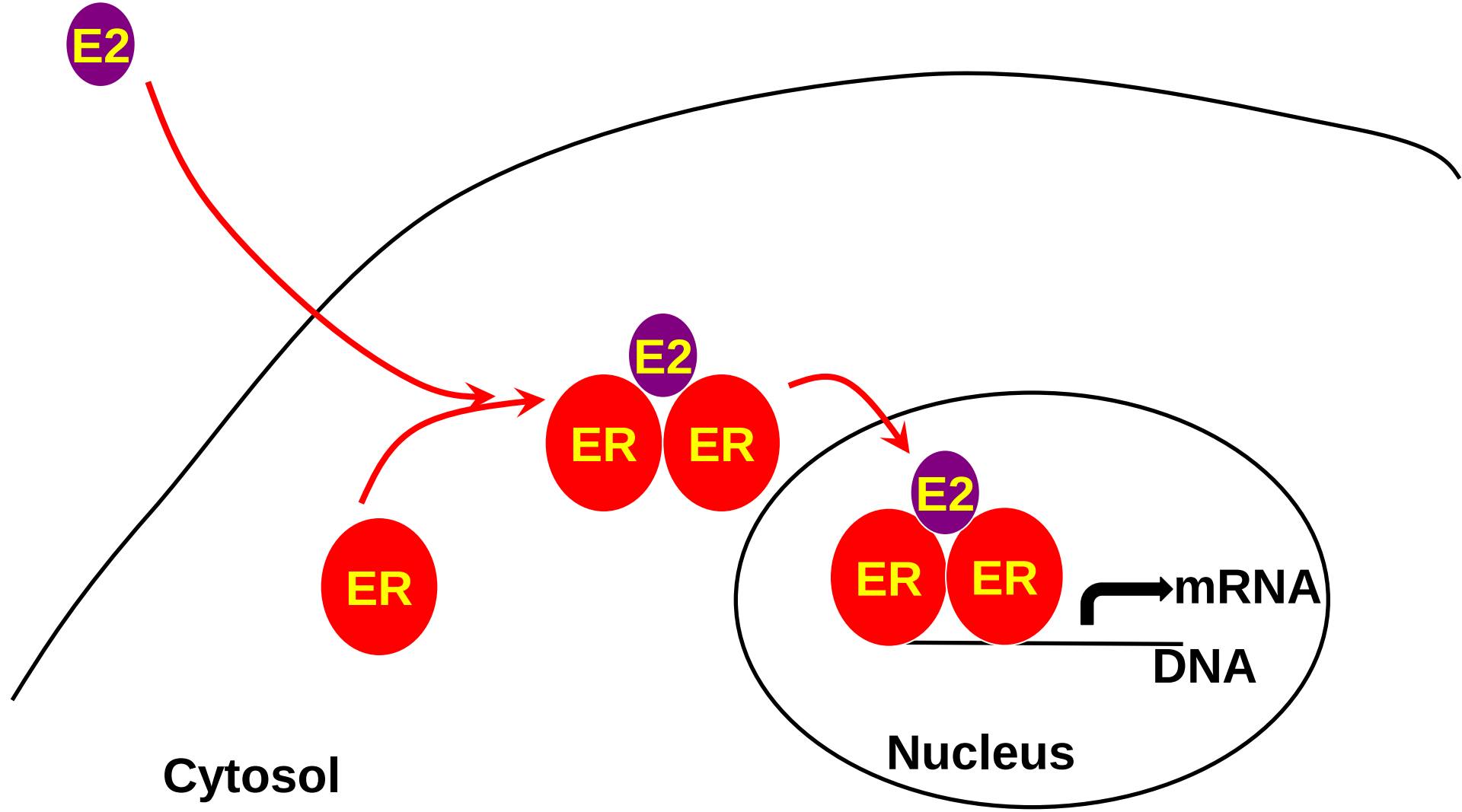
Patient underwent radical mastectomy

3 months later presented with diffuse chest wall and skin involvement with tumor and apparent metastatic disease in her thyroid

Patient underwent oophorectomy 1 month later and had a complete remission of her tumor and survived for 4 years

The First Therapy Based on Tumor Phenotype

Estrogen Receptor



The First Therapy Based on Tumor Genotype

HER2/Neu amplification

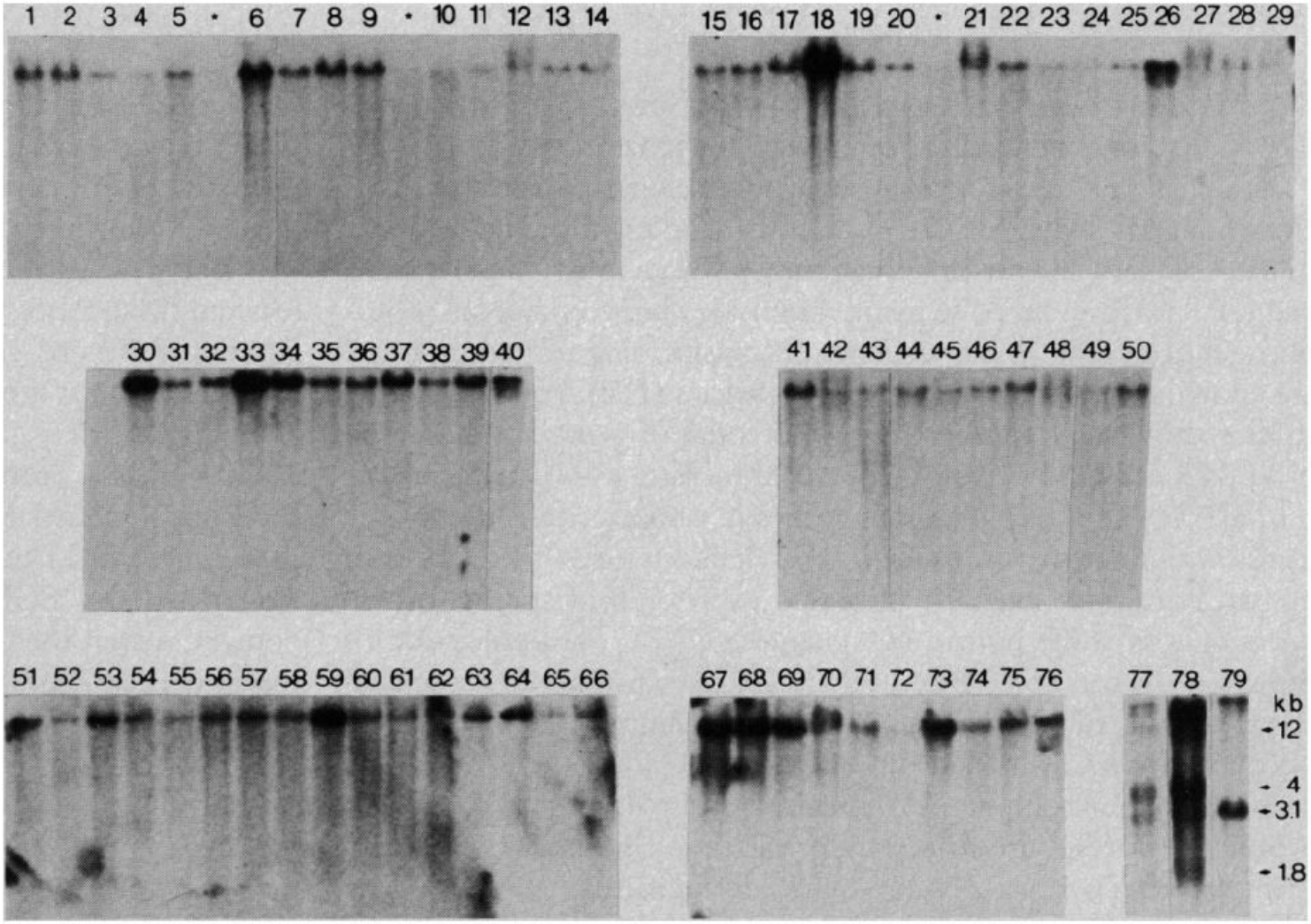
Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

Slamon *et al.*, Science 235: 177, 1987

The First Therapy Based on Tumor Genotype

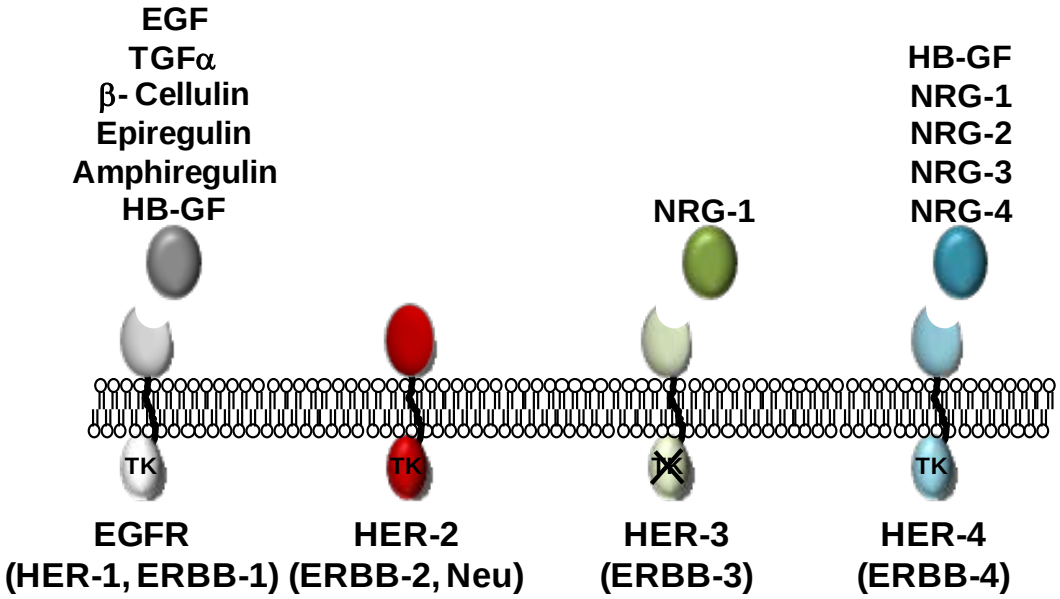
HER2/Neu amplification



Slamon *et al.*, Science 235: 177, 1987

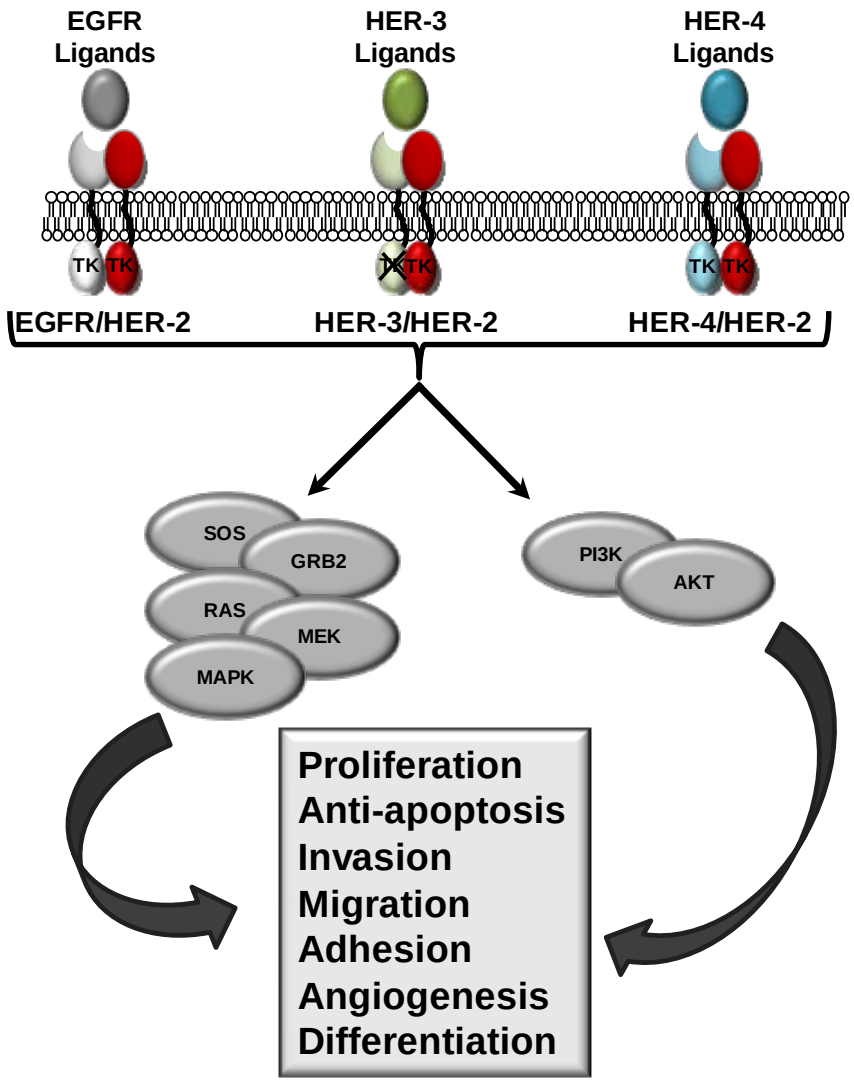
The First Therapy Based on Tumor Genotype

HER2/Neu amplification



The First Therapy Based on Tumor Genotype

HER2/Neu amplification



Genomic Medicine and Breast Cancer Present

Treatment based on:

Clinical features of the tumor
(size, pathologic grade, nodal metastasis)

Expression and/or genetic abnormalities of multiple genes in the tumor

- **Estrogen Receptor and Progesterone Receptor**
- **HER2/Neu Amplification**
- **Recurrence Score**
- **Gene Expression Microarrays**

Recurrence Score

Developed to stratify the risk of relapse and/or need for chemotherapy

- **Early stage**
- **Hormone receptor positive tumors**
- **Node negative**
- **Tamoxifen treated**

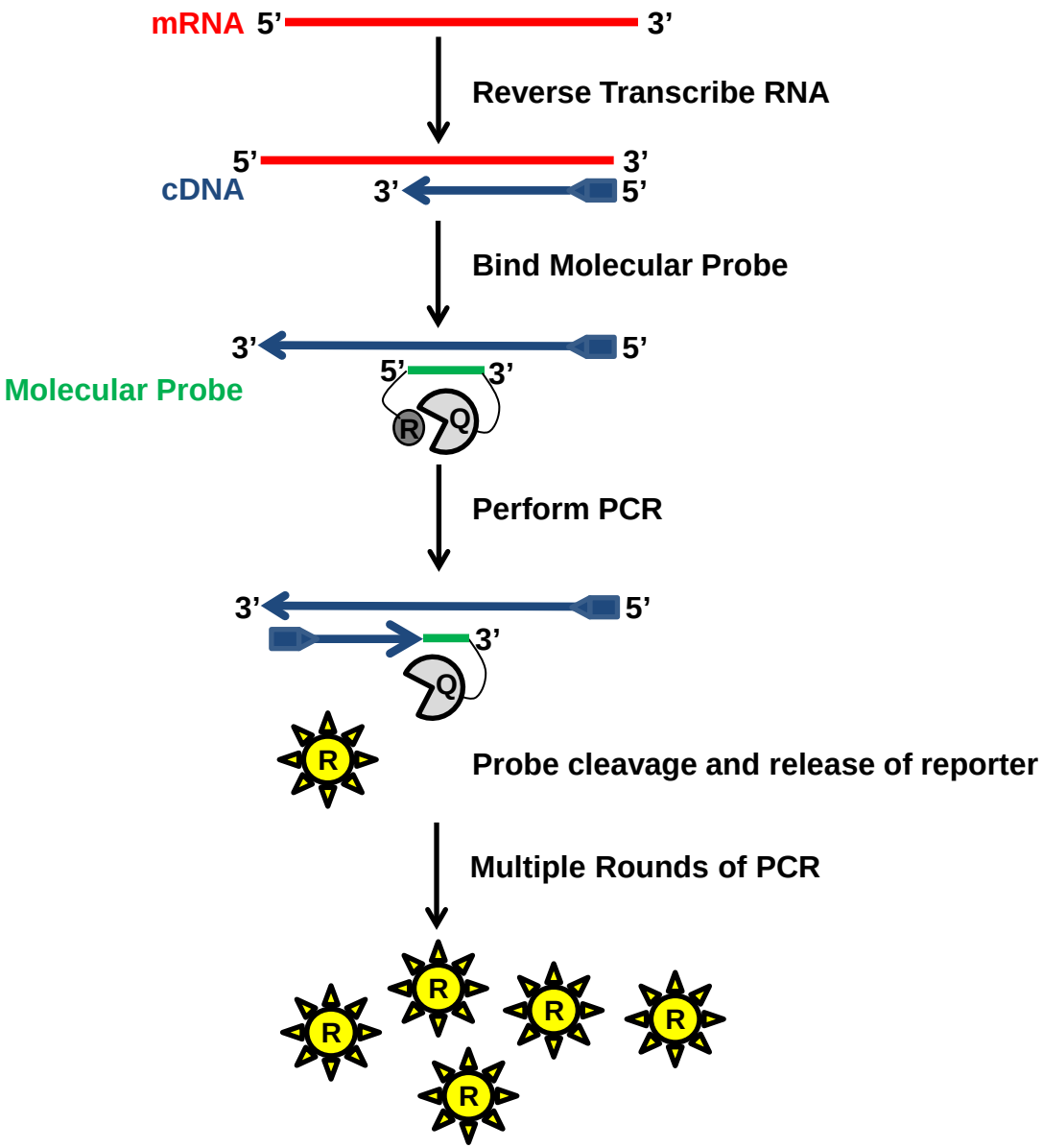
21 Gene set developed from literature and array experiments

Designed to use Quantitative Reverse Transcription PCR (qRT-PCR) of RNA from formalin fixed paraffin-embedded tumor tissue

Paik *et al*., N Engl J Med 351: 2817, 2004

Recurrence Score

Quantitative Reverse Transcription PCR



Recurrence Score

mRNA Targets

ESTROGEN
ER
PR
Bcl2
SCUBE2

HER2
GRB7
HER2

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

INVASION
Stromolysin 3
Cathepsin L2

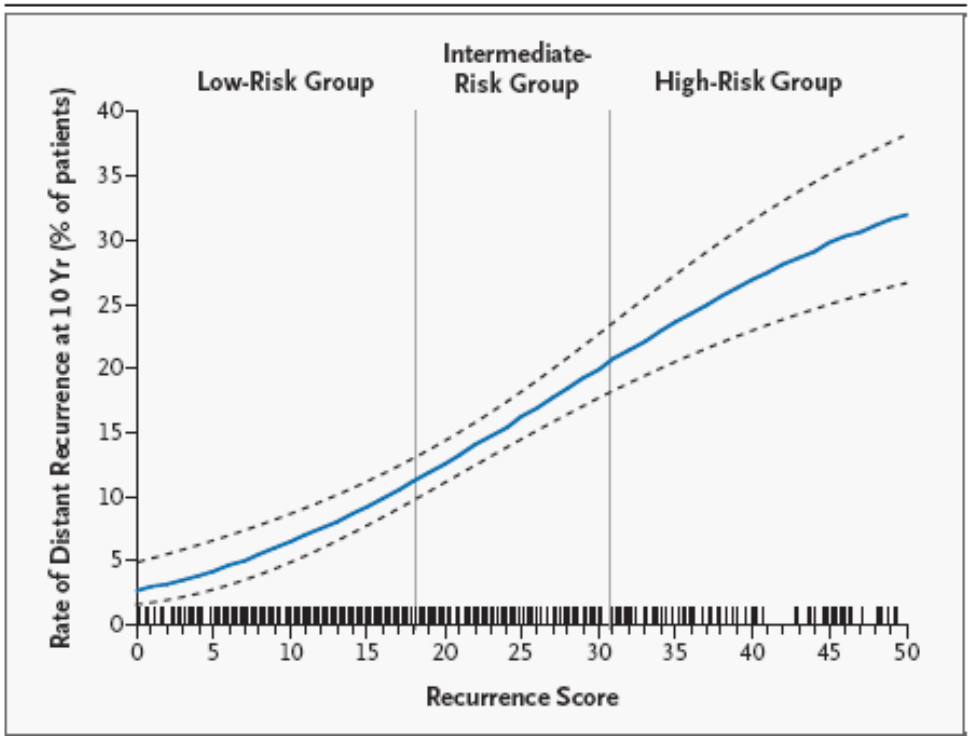
OTHER
GSTM1
CD68
BAG1

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

Paik *et al*., N Engl J Med 351: 2817, 2004

Recurrence Score

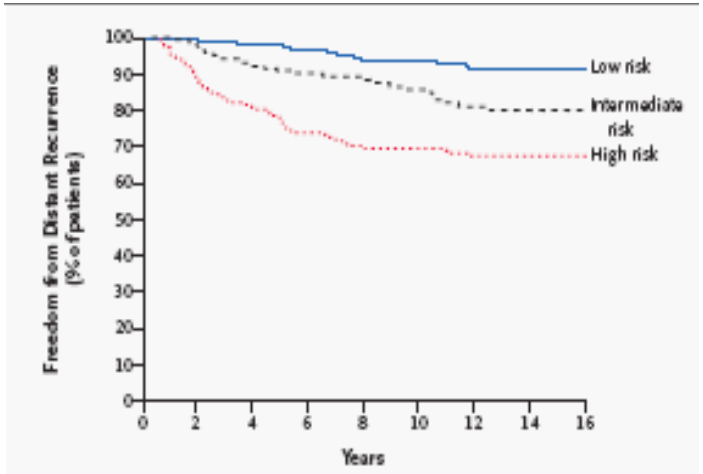
Continuous Predictor of Recurrence



Paik *et al*., N Engl J Med 351: 2817, 2004

Recurrence Score

Prognosis



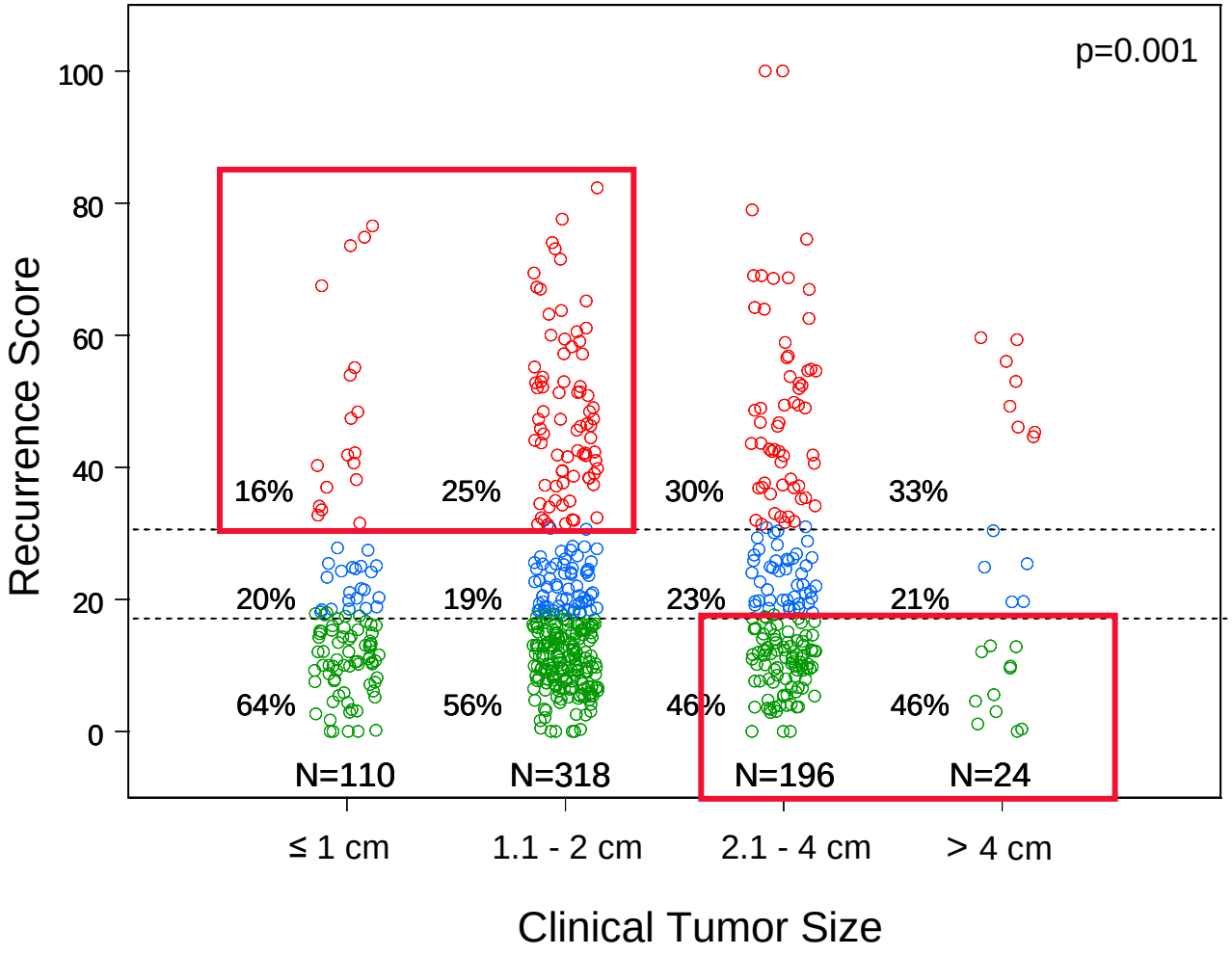
Risk	Score	% Pts	RR at 10y
Low (338)	RS≤17	51	6.8
Intermediate (149)	RS 18-30	22	14.3
High (181)	RS≥31	27	30.5

p<0.00001

Paik *et al*., N Engl J Med 351: 2817, 2004

Recurrence Score

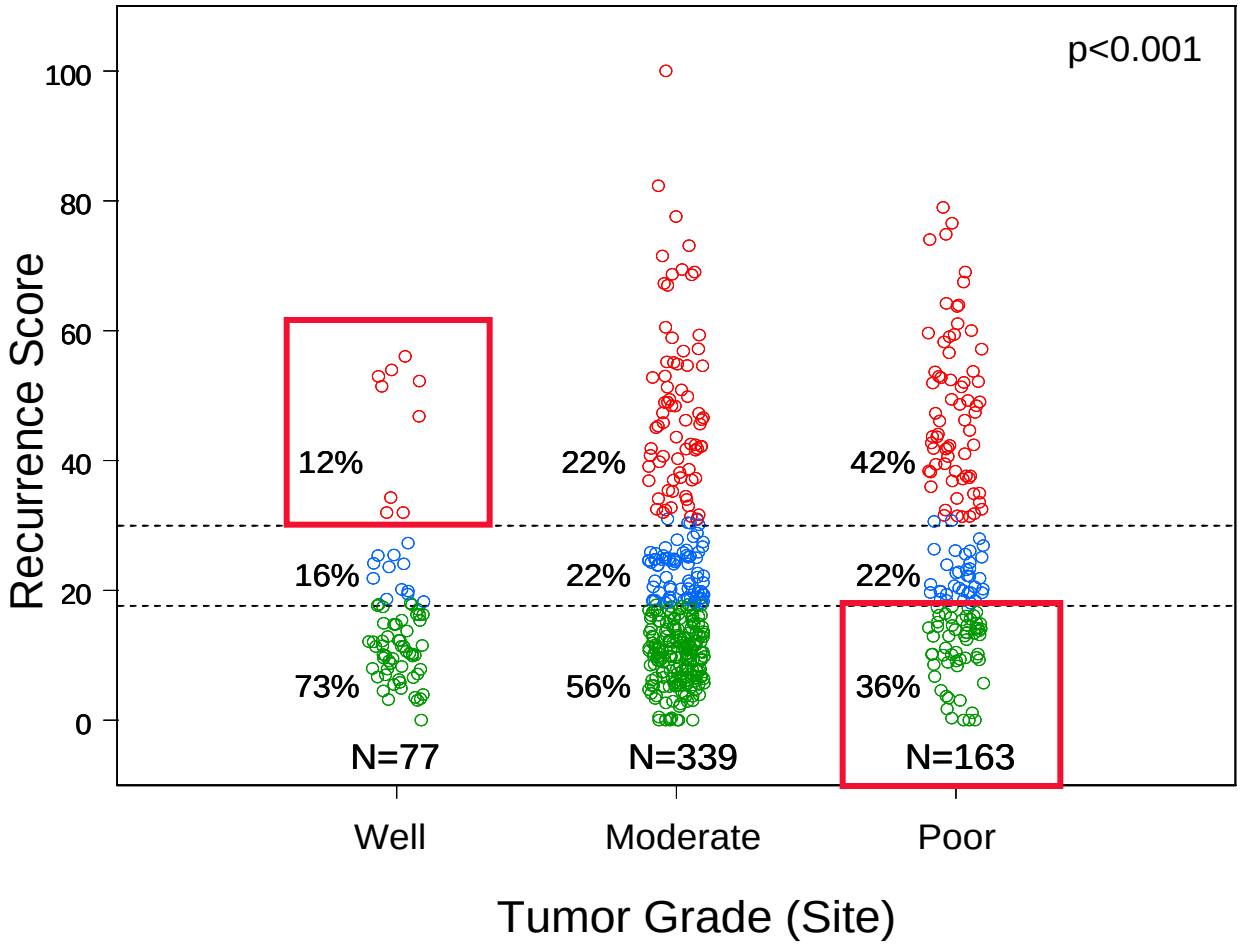
Tumor Size



Paik *et al.*, J Clin Oncol 24: 3726, 2006

Recurrence Score

Tumor Grade



Paik *et al.*, J Clin Oncol 24: 3726, 2006

Recurrence Score

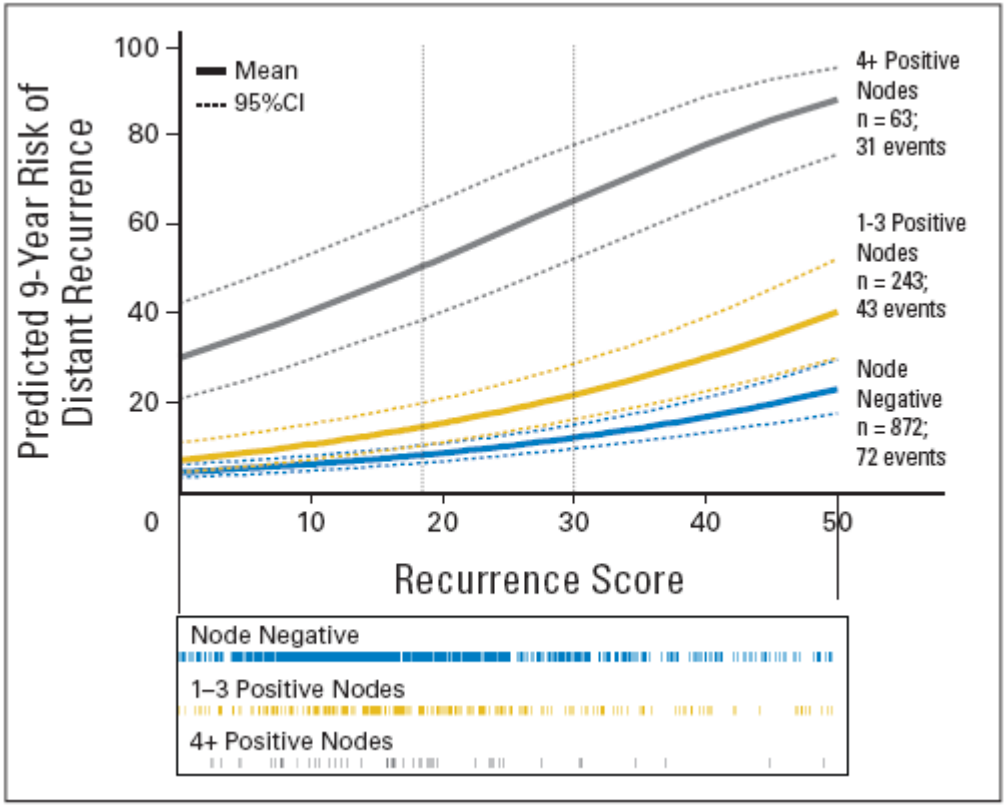
HER2/Neu Amplification

Oncotype Risk Group	HER2/Neu Amplified	HER2/Neu Not Amplified	Total
Low Risk	0	334	334
Intermediate Risk	5	142	147
High Risk	50	129	179
Total	55	605	660

Paik S: ASCO 2006

Recurrence Score

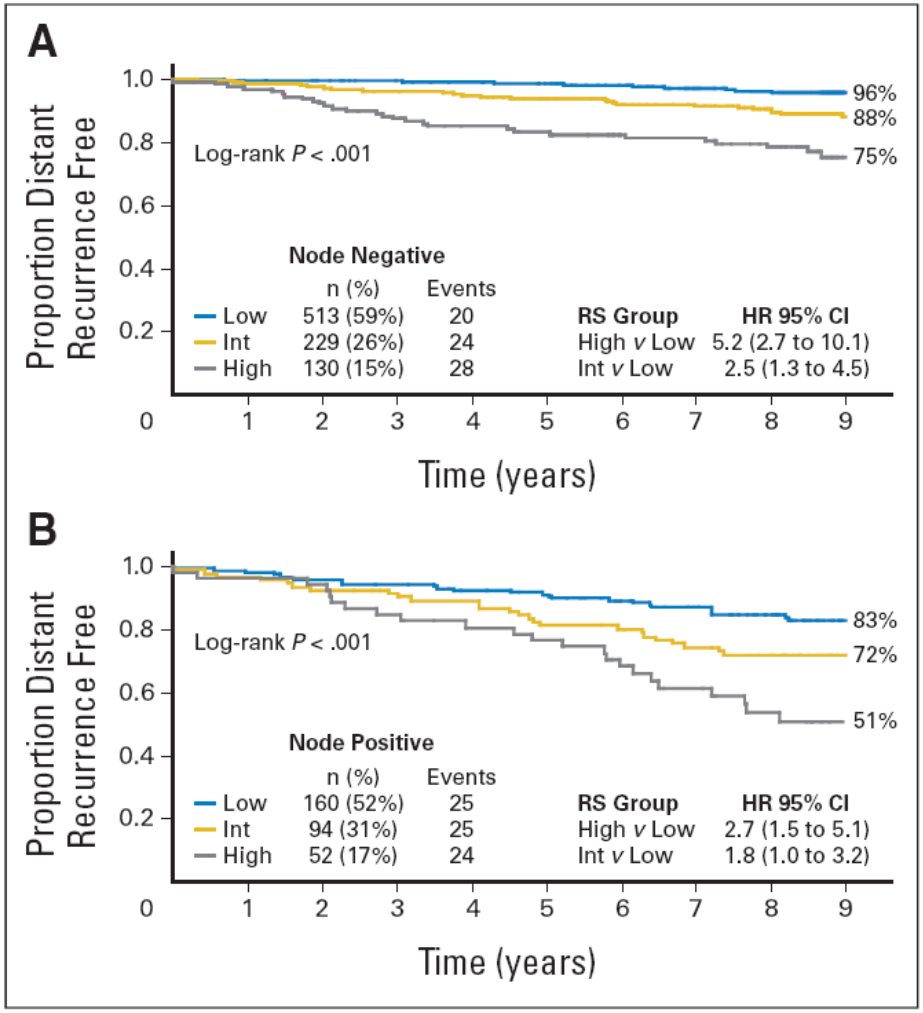
Node Positive Tumors



Dowsett *et al.*, J Clin Oncol 28: 1829, 2010

Recurrence Score

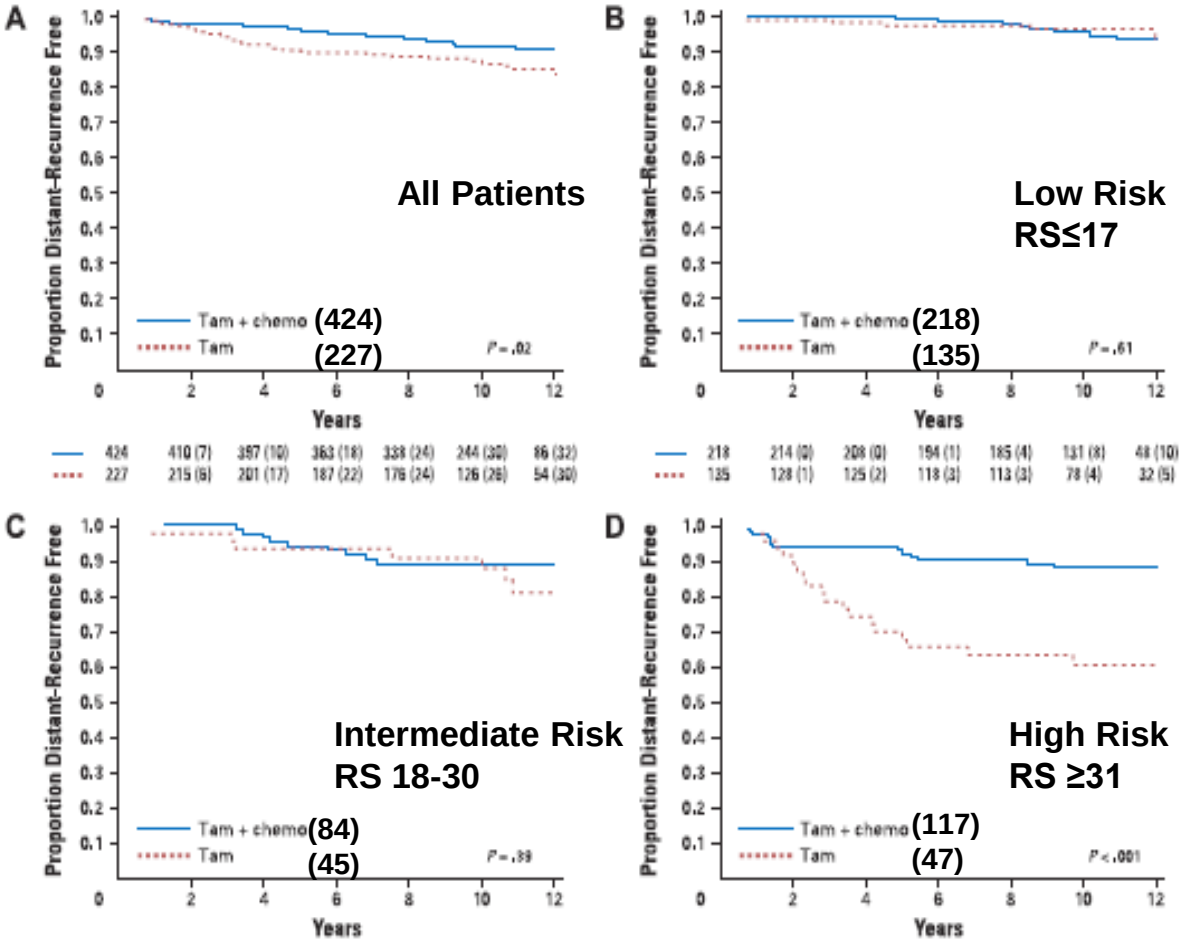
Node Positive Tumors



Dowsett *et al.*, J Clin Oncol 28: 1829, 2010

Recurrence Score and Chemotherapy

Node Negative Tumors



Paik *et al.*, J Clin Onc 24: 3726, 2006

Gene Expression Microarrays

MammaPrint

Developed to predict risk of relapse in early stage patients

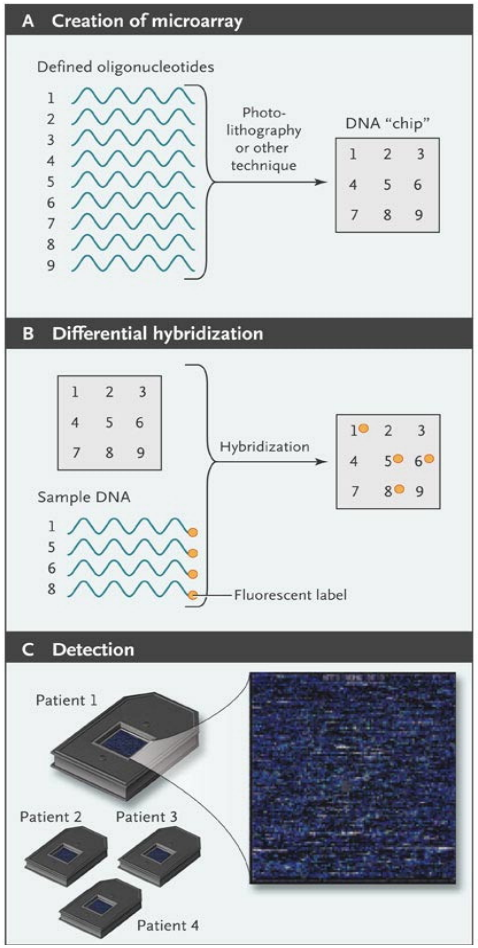
- **Early stage**
- **Hormone receptor postive and negative**
- **Node positive and negative**

70 gene set developed from cDNA microarray of ~25,000 genes

van't Veer *et al.*, Nature, 415, 530, 2002
Van der Vijvir *et al.*, N Engl J Med 347, 1999, 2002

Gene Expression Microarrays

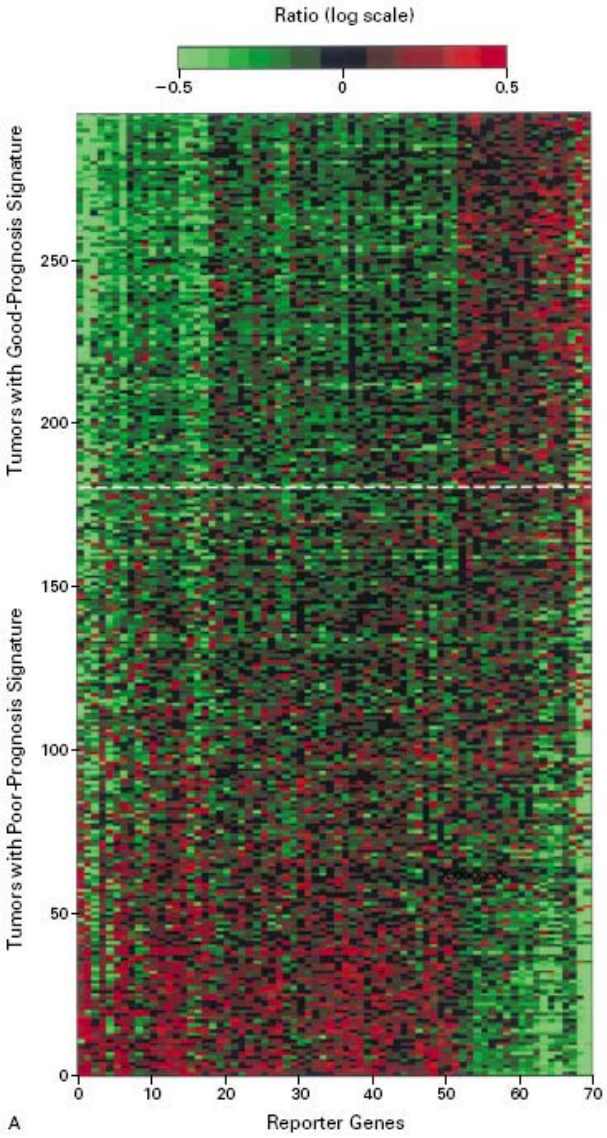
Microarray Technology



Feero WG *et al.,* N Engl J Med 362: 2001, 2010

Gene Expression Microarrays

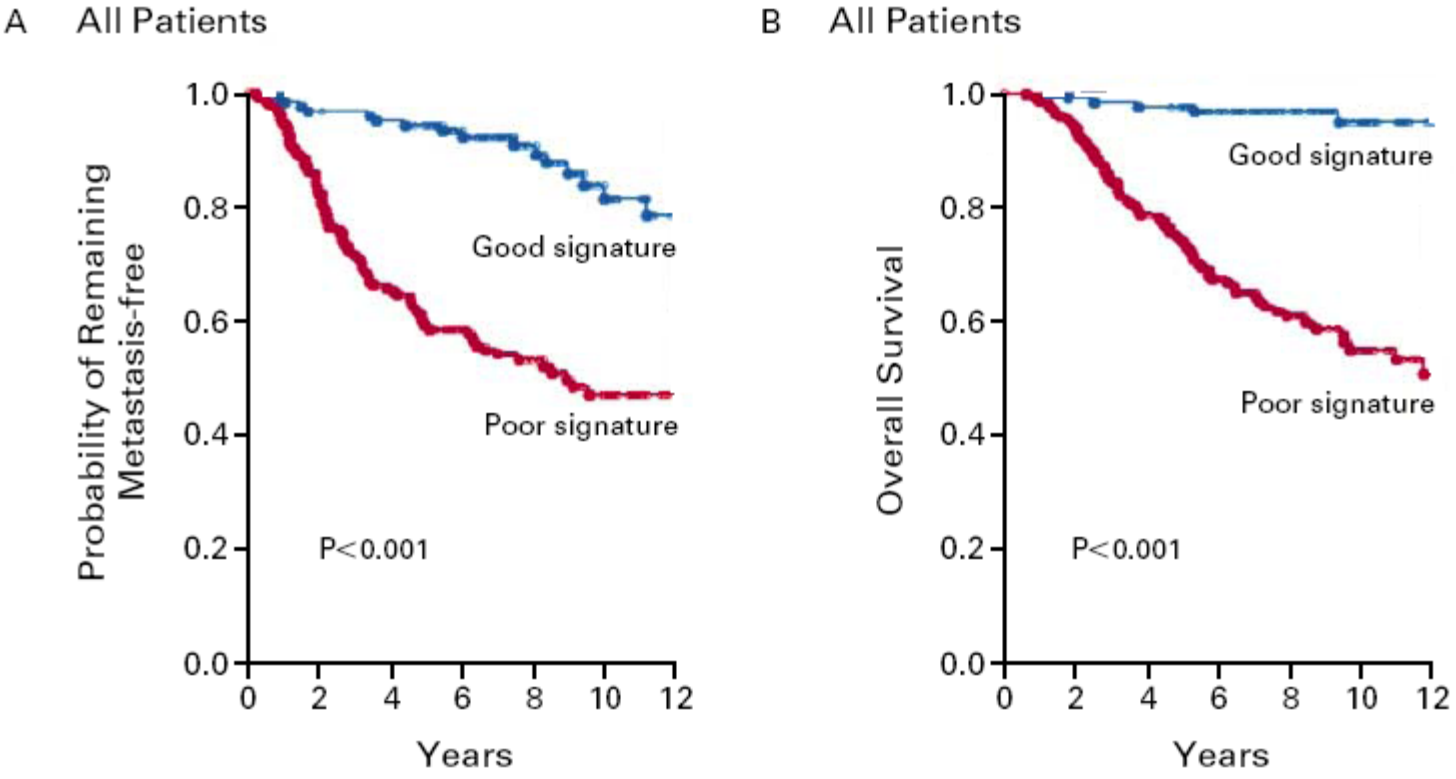
Mammaprint



Van der Vijvir *et al.*, N Engl J Med 347: 1999, 2002

Gene Expression Microarrays

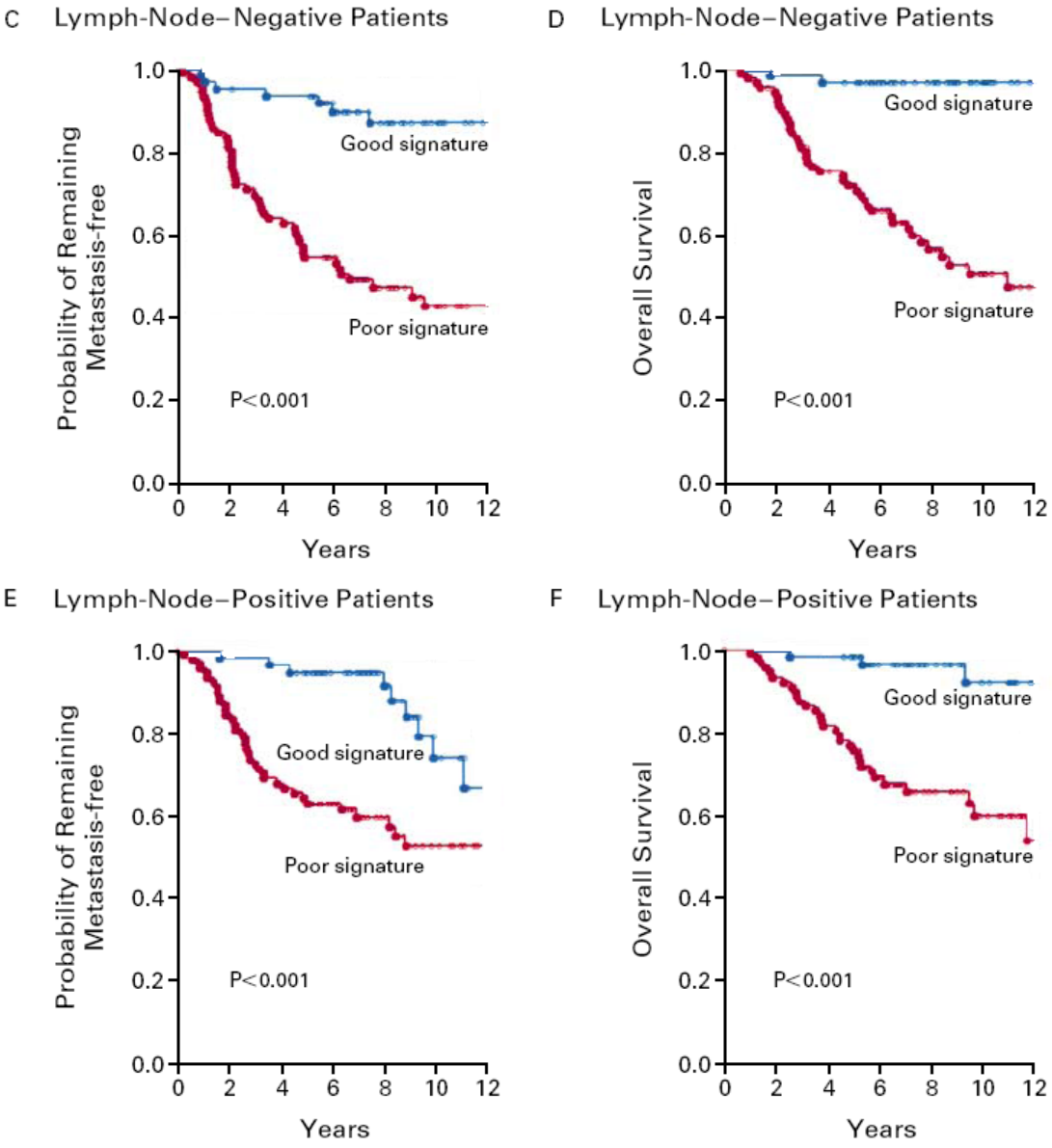
Mammaprint



Van der Vijvir *et al.*, N Engl J Med 347, 1999, 2002

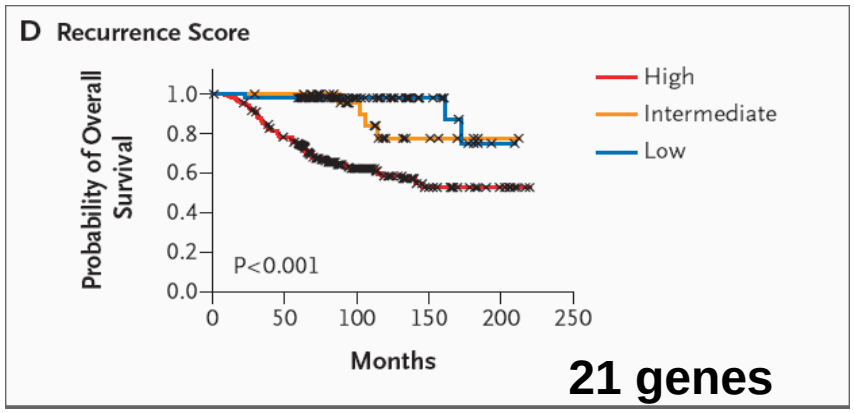
Gene Expression Microarrays

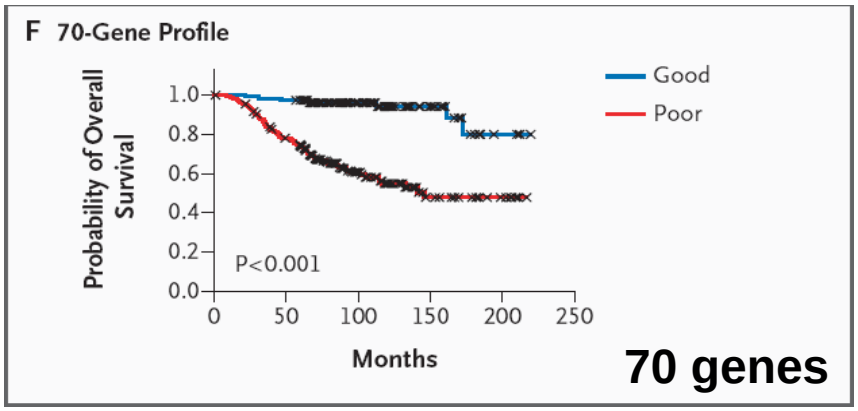
Mammaprint

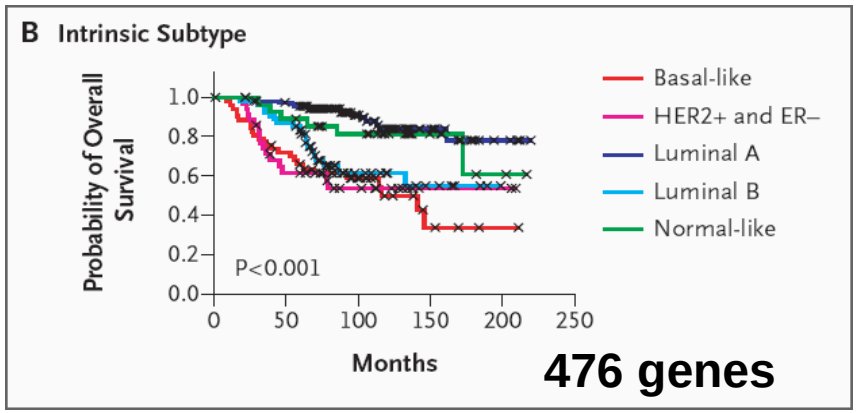


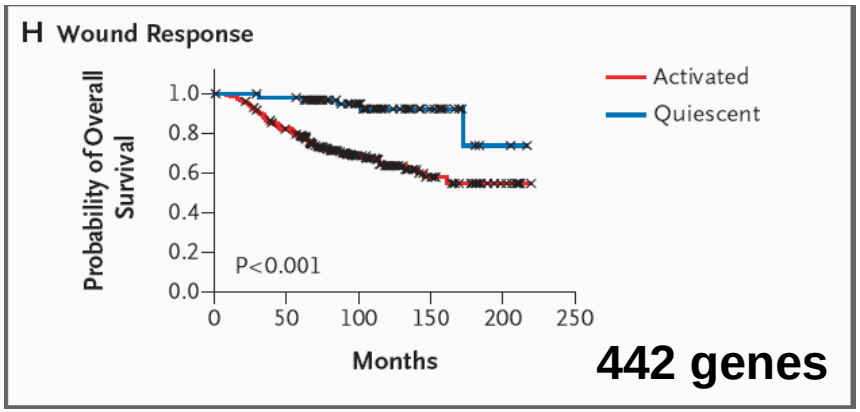
Van der Vijvir *et al.*, N Engl J Med 347, 1999, 2002

Comparison of Molecular Classifications of Breast Cancer









Fan *et al.*, N Engl J Med 355: 560, 2006

Genomic Medicine and Breast Cancer Future

Treatment based on:

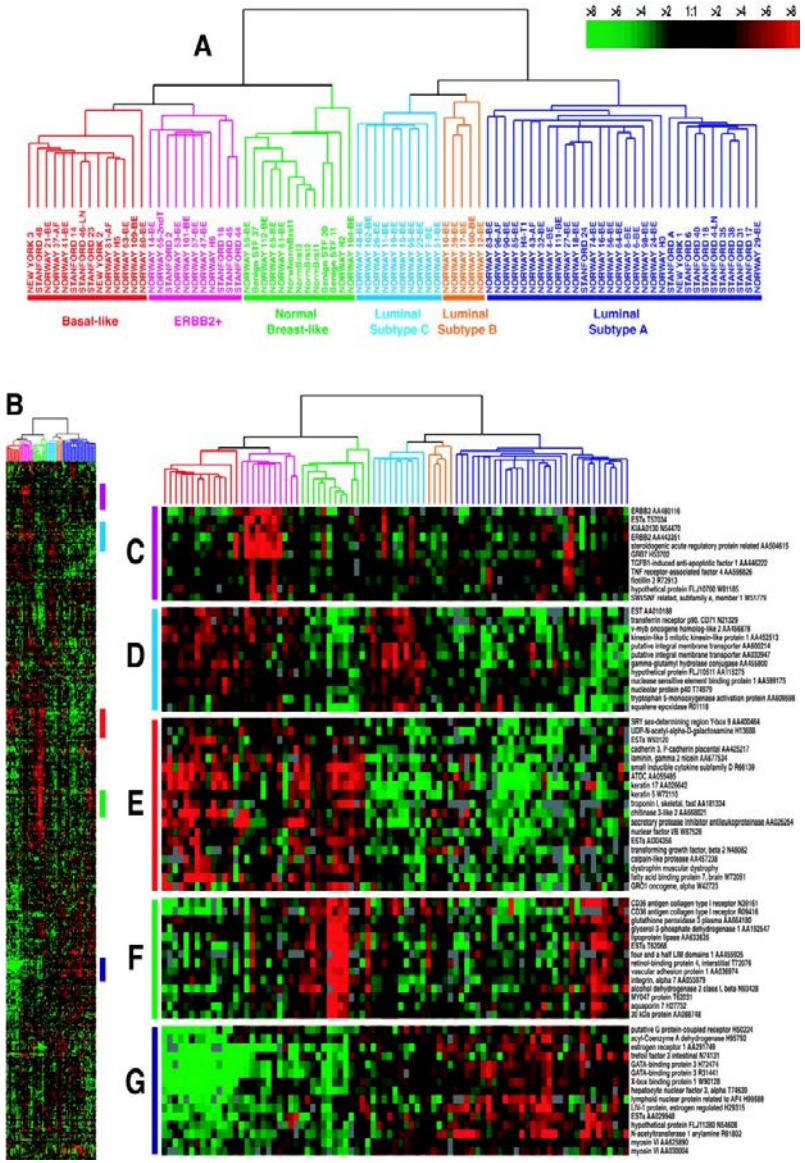
Clinical features of the tumor
(size, pathologic grade, nodal metastasis)

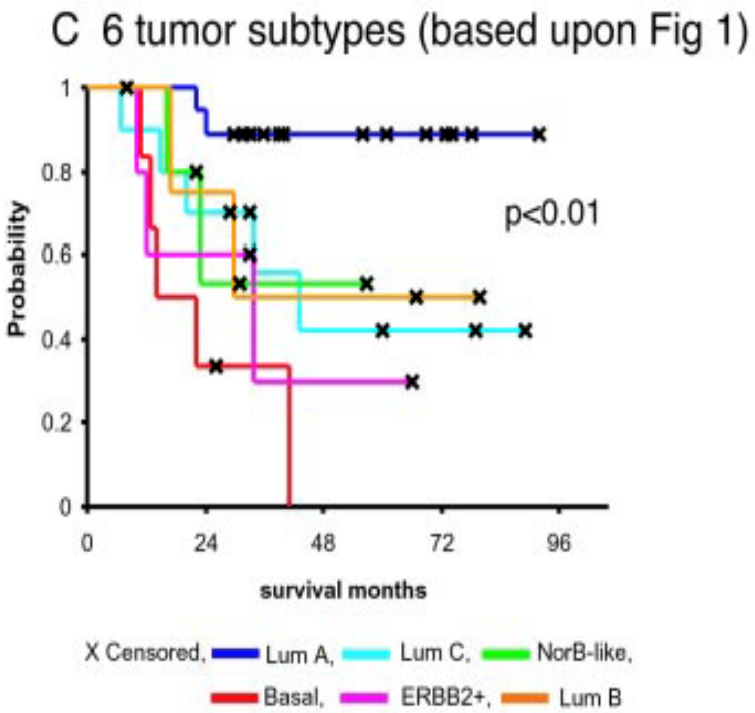
Expression and/or genetic abnormalities of multiple genes in the tumor

- **Estrogen Receptor and Progesterone Receptor**
- **HER2/Neu Amplification**
- **Measures of multiple gene expression**
- **Pharmacogenomics**
- **Whole genome sequencing**

Expression Profiling of Breast Cancer

Intrinsic subtypes

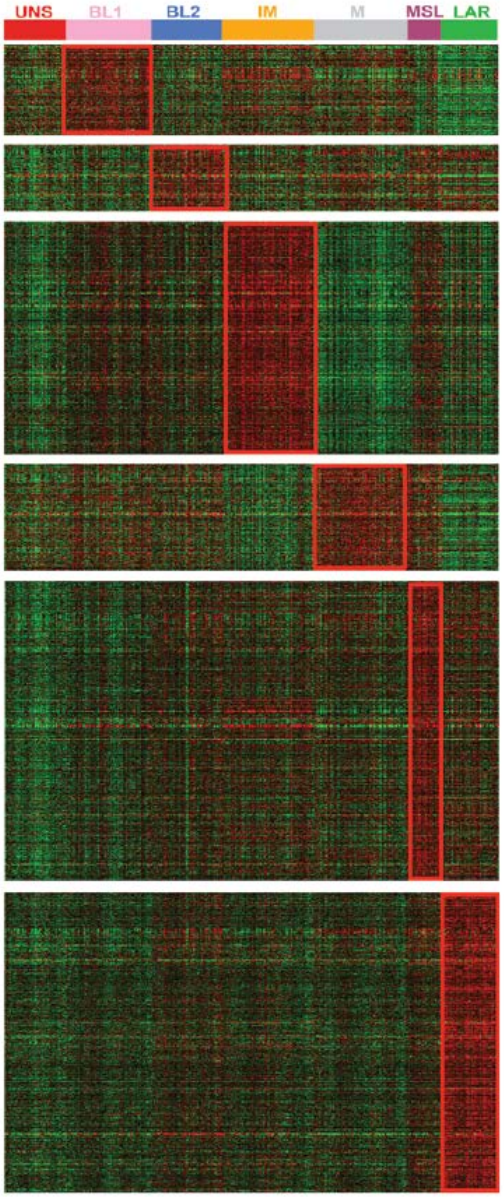




Sorlie *et al.*, Proc Natl Acad Sci U S A. 98:10869, 2001

Molecular Profiling of Breast Cancer

Triple Negative Breast Cancer



Lehmann *et al.*, J Clin Invest 121: 2767, 2011

Pharmacogenomics

Using genetic information (genotype or phenotype) to predict drug efficacy or toxicity

Pharmacogenomics

Using genetic information (genotype or phenotype) to predict drug efficacy or toxicity

In Cancer Biology there are two genomes

Tumor (somatic)

Patient (germline)

Pharmacogenomics

Tumor Pharmacogenomics:

Presence of the therapeutic target predicts treatment benefit

- **Estrogen Receptor**
- **HER2/Neu amplification**

Pharmacogenomics

Tumor Pharmacogenomics:

Presence of the therapeutic target predicts treatment benefit

Estrogen Receptor → **Anti-hormonal agents**

HER2/Neu amplification → **Anti-HER2/Neu agents**

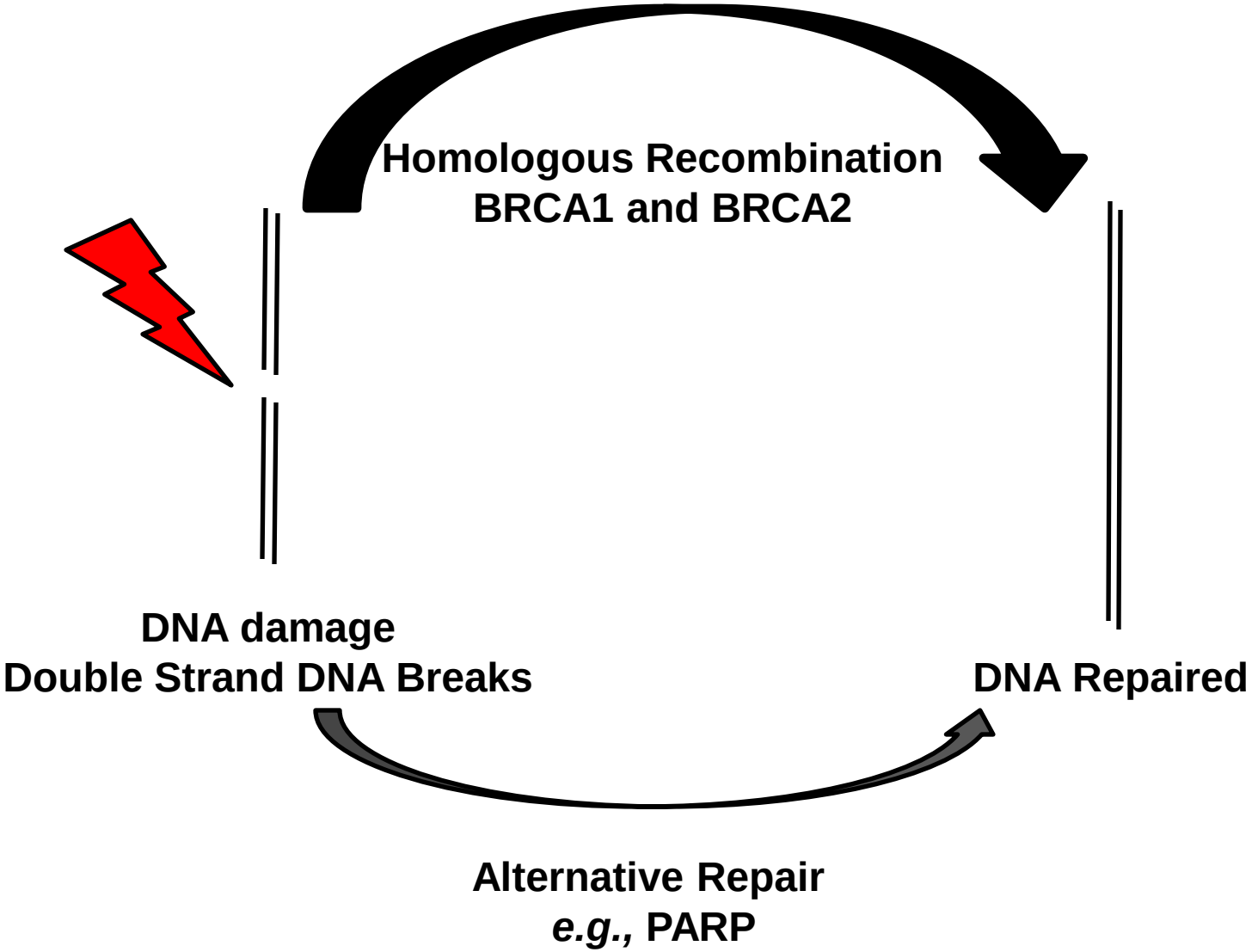
Pharmacogenomics

Tumor Pharmacogenomics:

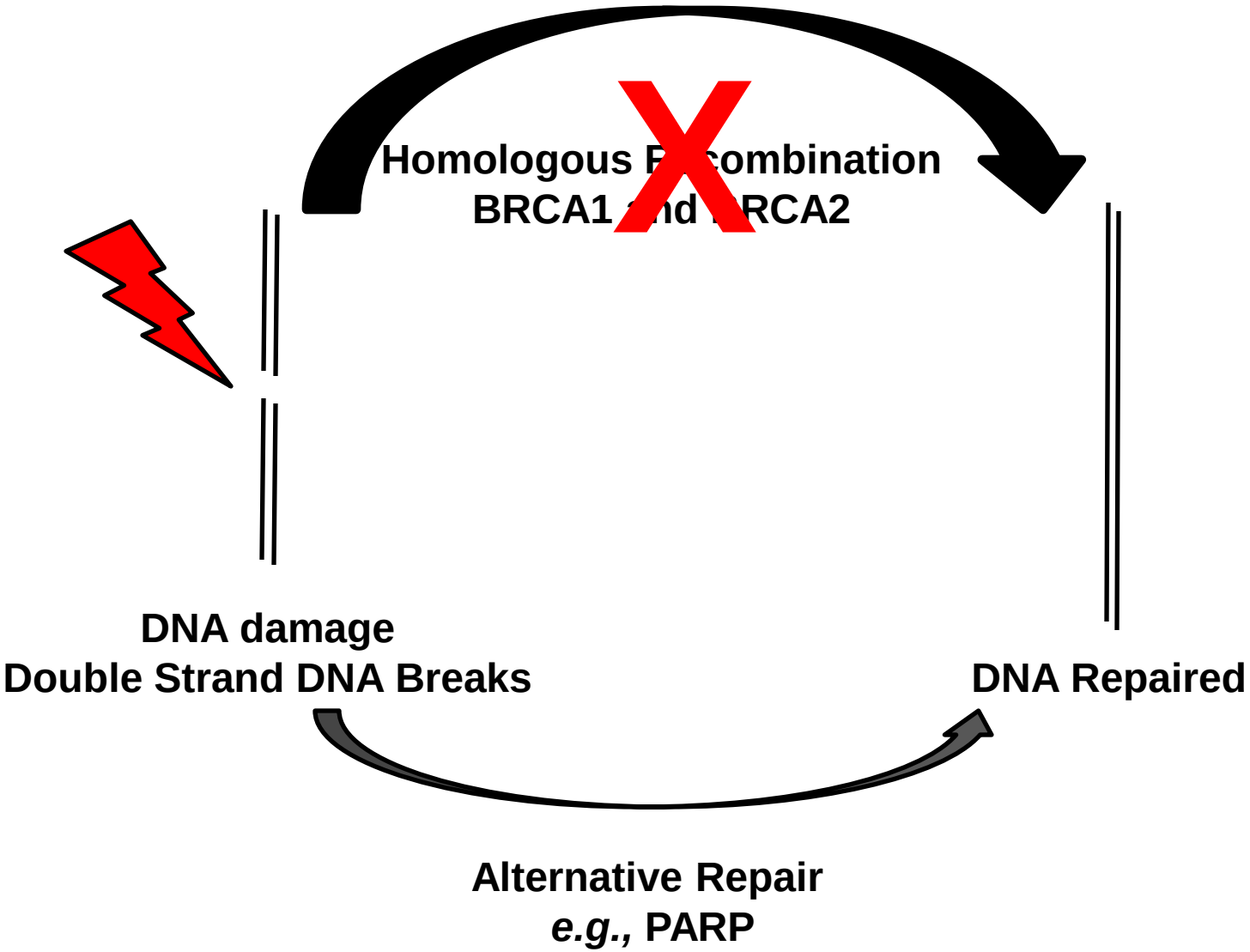
Genetic abnormality that predicts a treatment benefit

BRCA1 and BRCA2 mutations

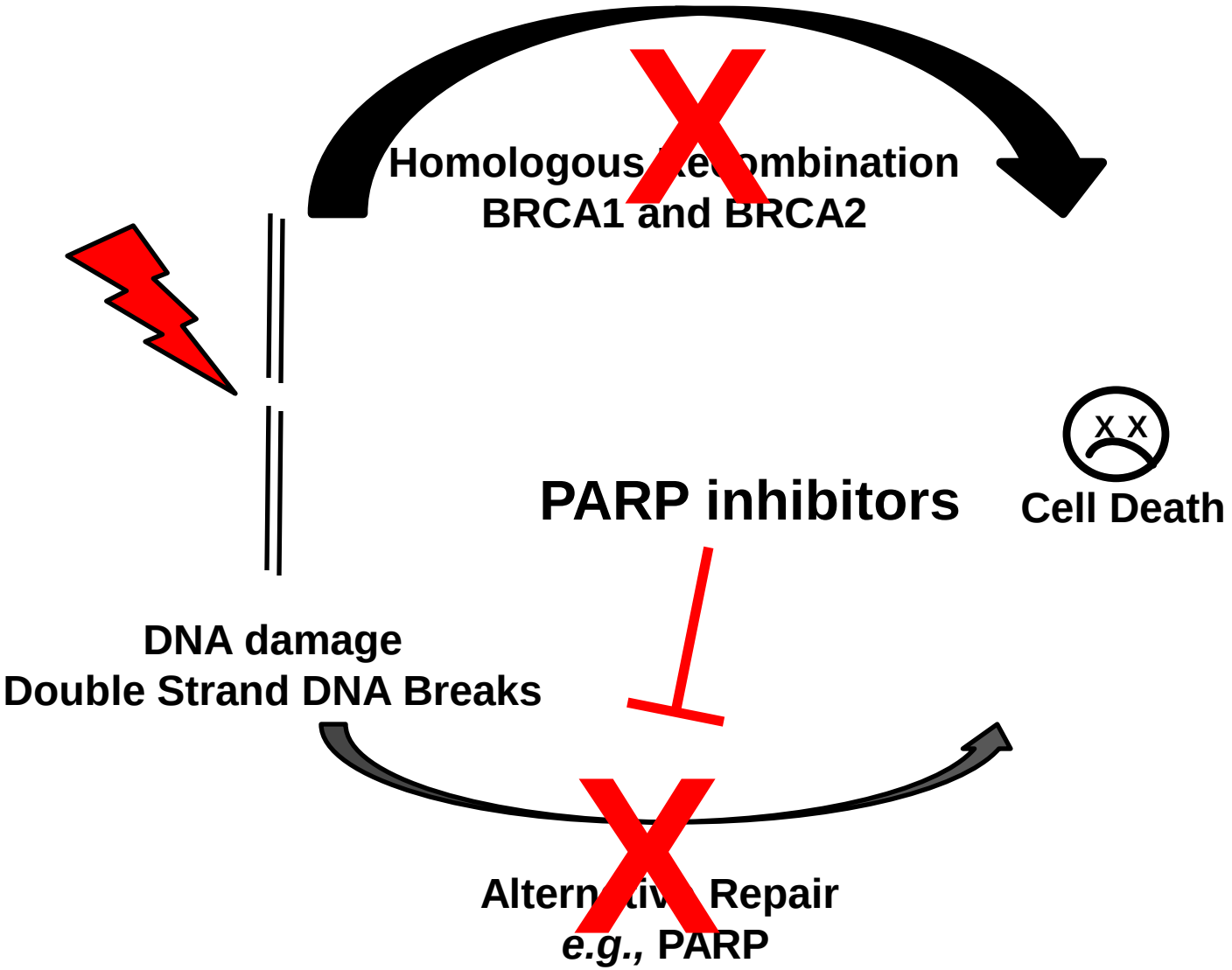
Pharmacogenomics



Pharmacogenomics



Pharmacogenomics



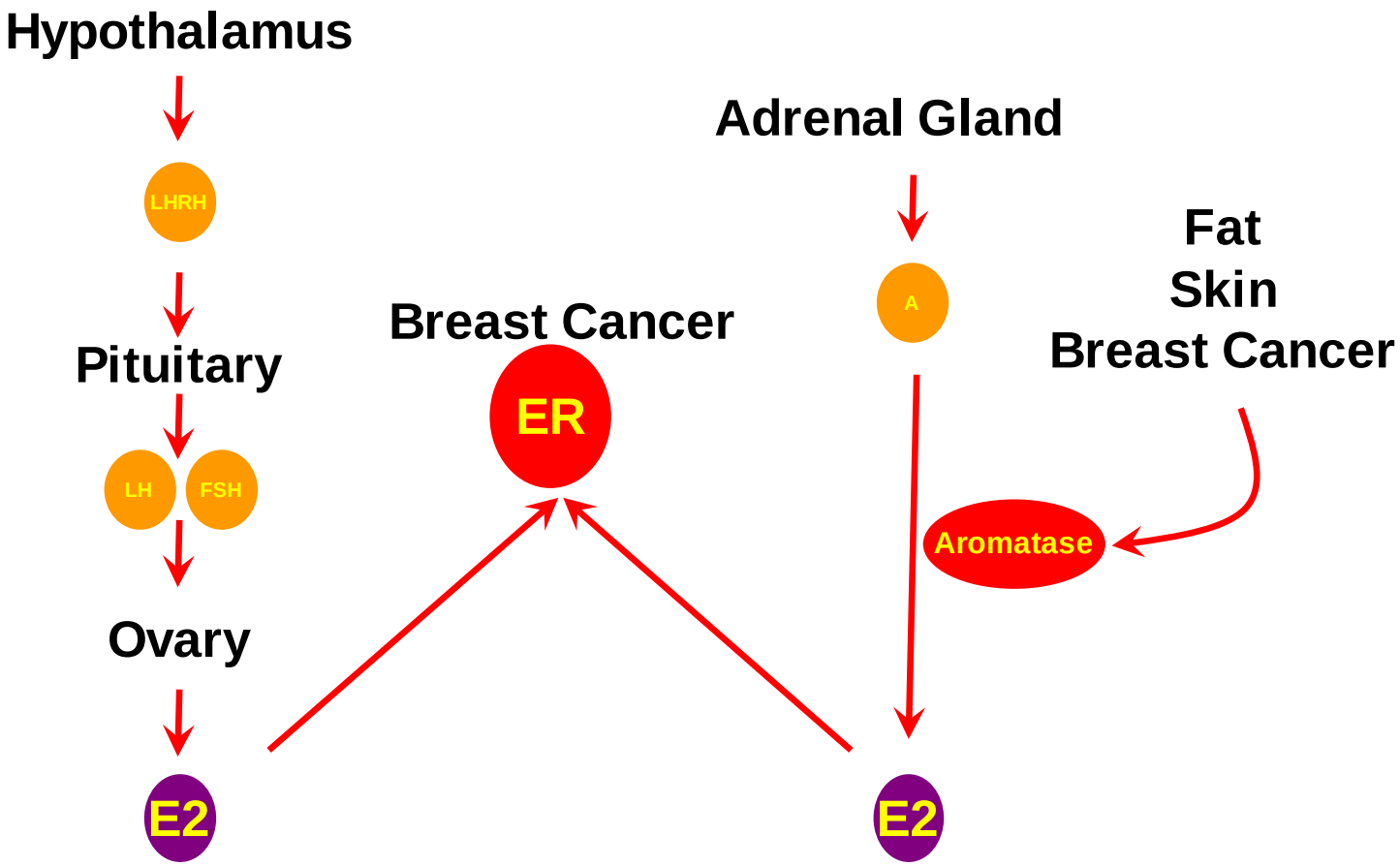
Pharmacogenomics

Patient Pharmacogenomics:

Presence of genotypic or phenotypic markers in the patient that predict a drugs efficacy or toxicity

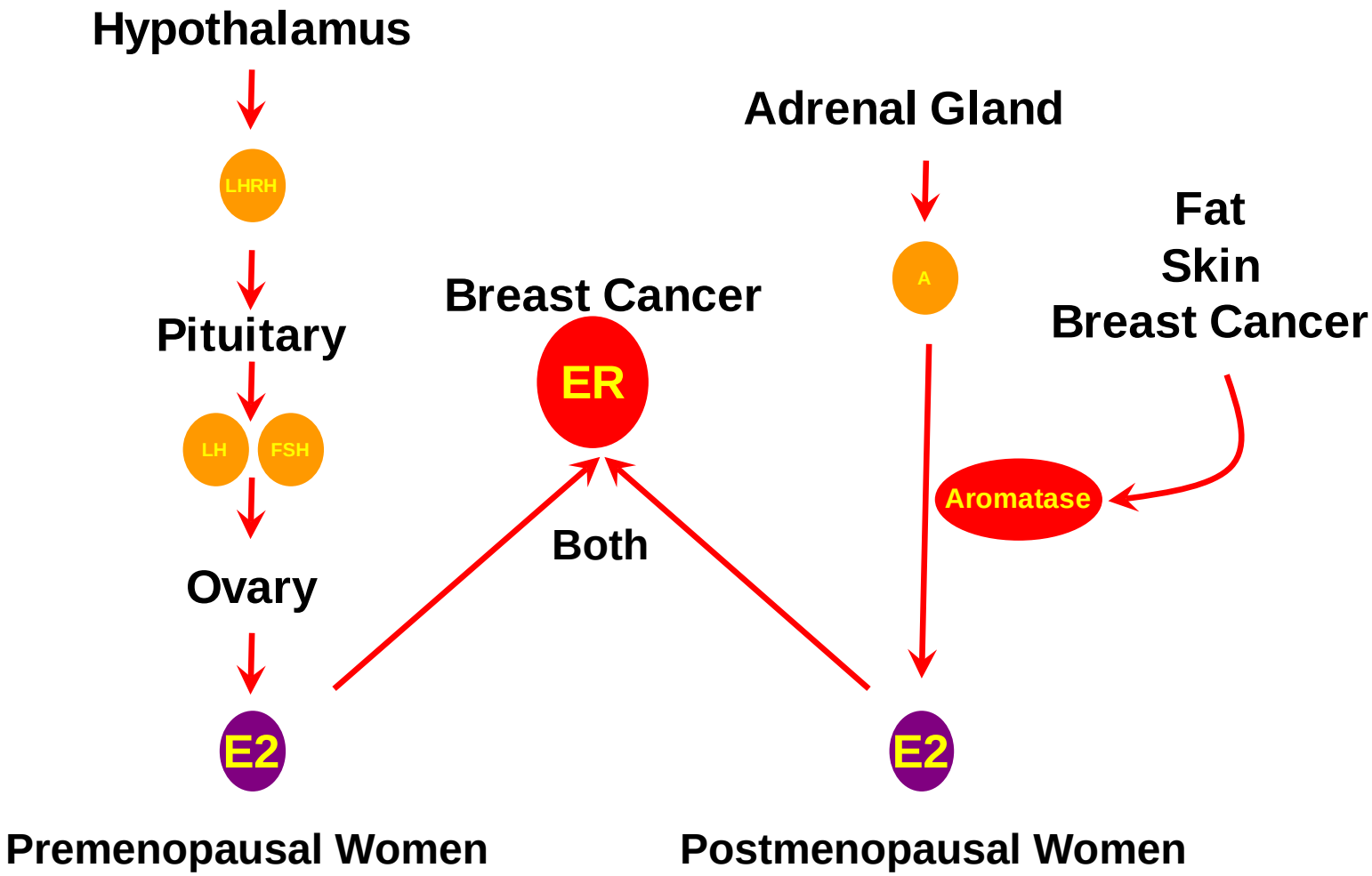
Patient Pharmacogenomics

Phenotype and Hormonal Treatment



Patient Pharmacogenomics

Phenotype and Hormonal Treatment



Pharmacogenomics

Patient Pharmacogenomics:

Presence of genotypic or phenotypic markers in the patient that predict a drugs efficacy

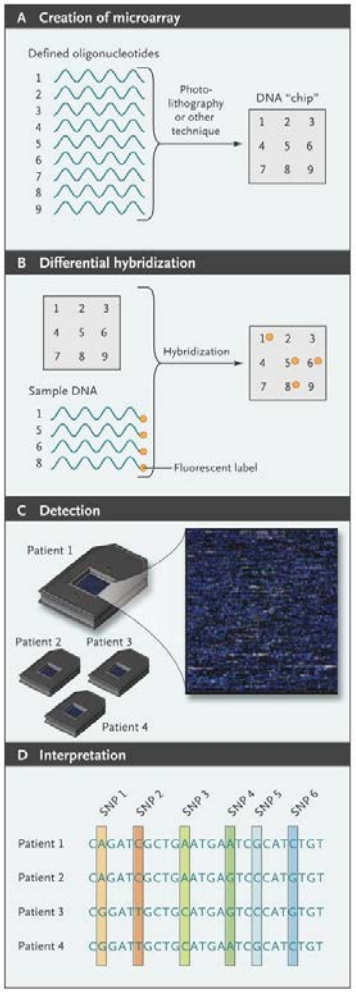
Metabolic enzyme isotypes may affect metabolism of drugs

_e.g._, cytochrome p450 enzymes

Most commonly single nucleotide polymorphisms (SNPs)

Genomic Sequence Variation

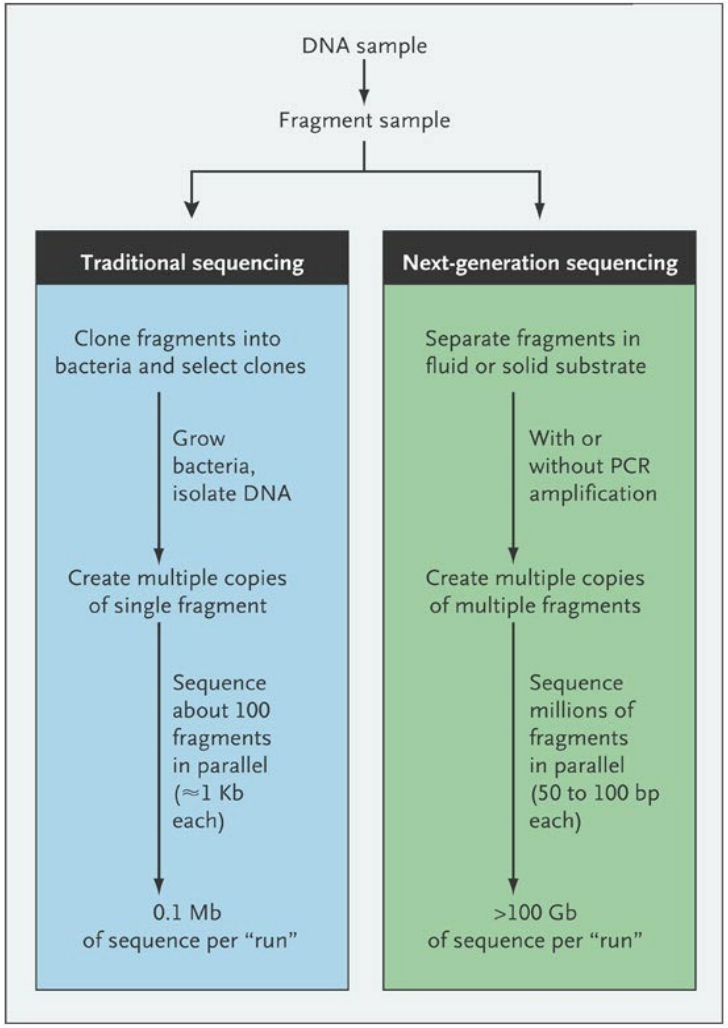
Single Nucleotide Polymorphism (SNP) Arrays



Feero WG et al. N Engl J Med 362: 2001, 2010

Genomic Sequence Variation

Whole Genome Sequencing



Feero WG et al. N Engl J Med 362: 2001, 2010

Genomic Sequence Variation

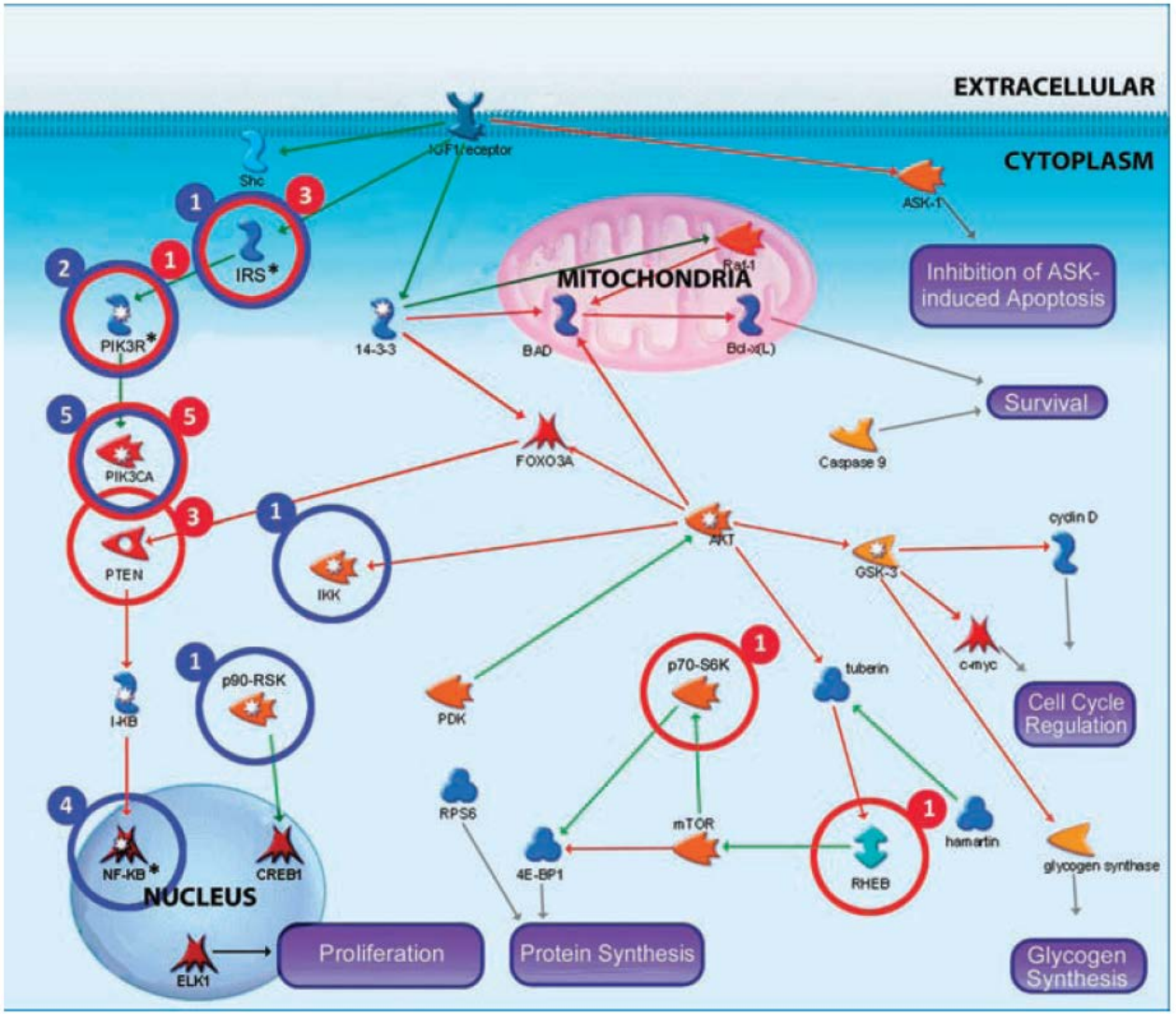
Whole Genome Sequencing

Wood et al., Science 318: 1108, 2007

Genomic Sequence Variation

Whole Genome Sequencing

PI3K Pathway Mutations



Wood et al., Science 318: 1108, 2007

Genomic Medicine and Breast Cancer Past, Present, and Future

Prognostic determination and treatment decisions

Past: **Tumor characteristics (size, grade, nodal metastasis)**
Expression or mutation of a few genes
***e.g.*, ER, PR, HER2/Neu**

Present: **Tumor characteristics (size, grade, nodal metastasis)**
Expression or mutation of a multiple genes primarily in the tumor
***e.g.*, Recurrence Score, Microarrays**

Future: **Tumor characteristics (size, grade, nodal metastasis)**
Expression or mutation of many (perhaps hundreds) of genes in the tumor and the patient
***e.g.*, Whole genome sequencing, SNP arrays**