Centre Jean PERRIN

Centre de Lutte contre le Cancer d'Auvergne

Clermont-Ferrand - France -

Molecular classifications of breast cancer

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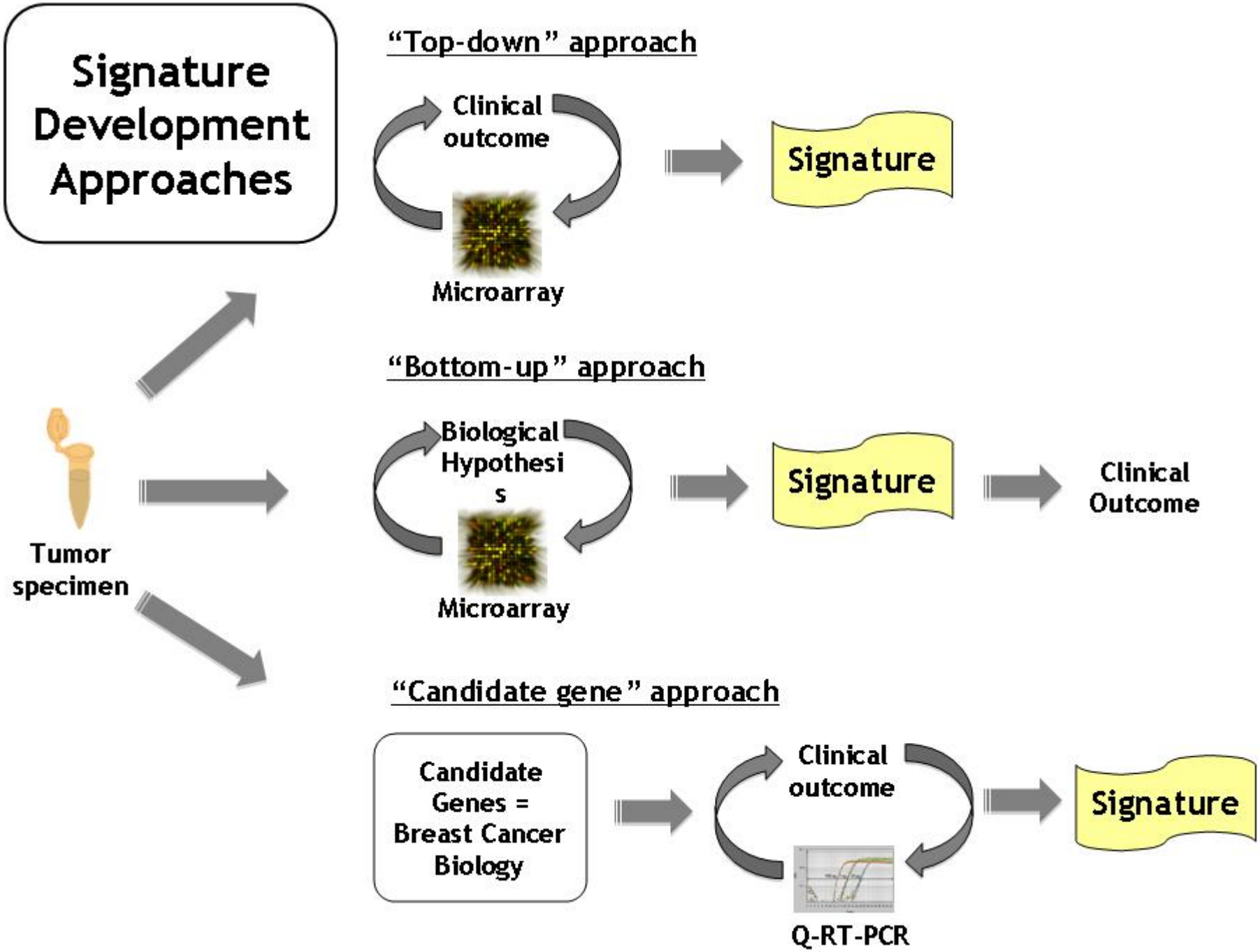
Fédération Nationale DES CENTRES DE LUTTE CONTRE LE CANCER

Centre JEAN PERRIN

Classical pathological prognosis and predictive factors.

- TNM parameters
- Grade
- Histological subtypes
- Tumor margins
- ER/PR and HER2 status


Signature Development Approaches
"Top-down" approach
Clinical outcome
Microarray
Signature
"Bottom-up" approach
Biological Hypothesis
Microarray
Signature
Clinical Outcome
Tumor specimen
"Candidate gene" approach
Candidate Genes = Breast Cancer Biology
Clinical outcome
Q-RT-PCR
Signature

Introduction

- For many years, breast cancer has been considered as an unique disease and treated as an unique disease based on clinical and pathological parameters
- During the last 20 years, extended knowledge of breast cancer biology, has put some light in our understanding of breast cancer
- High throughput technologies such as expression profiling has recently introduced new taxonomy of IBC

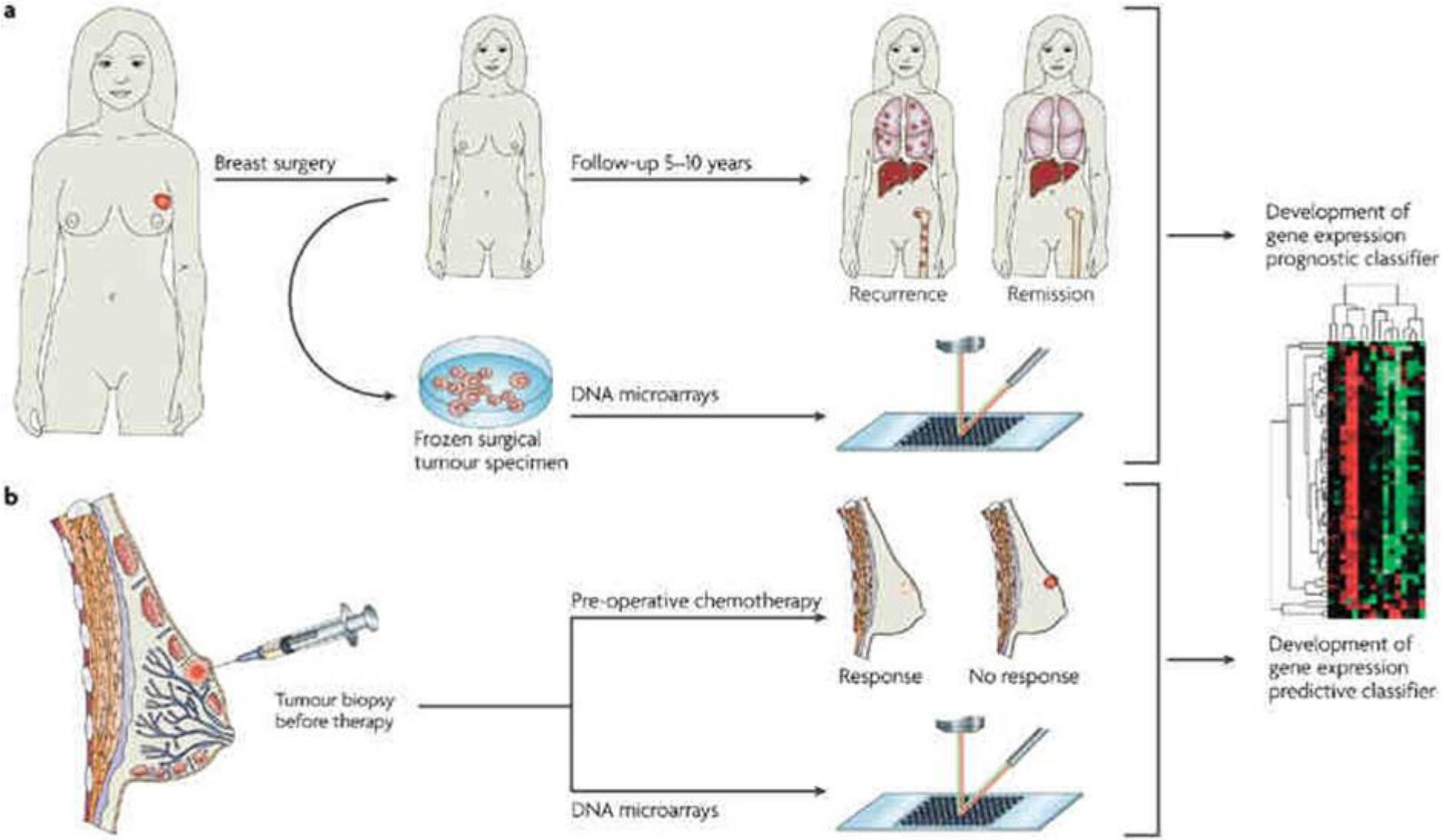
Outlines

- Perou and Sorlie's classification of BC
- Molecular grade
- Mammaprint
- OncotypeDX

Expression profiling : new classification

- Five distinct patterns of expression
  - 2 Luminal type ER+++, CK8-18
  - 1Basal-like: CK5-6, CK14
  - 1HER2 positive
  - 1 normal breast
    (adipose tissue, non epithelial cell types)

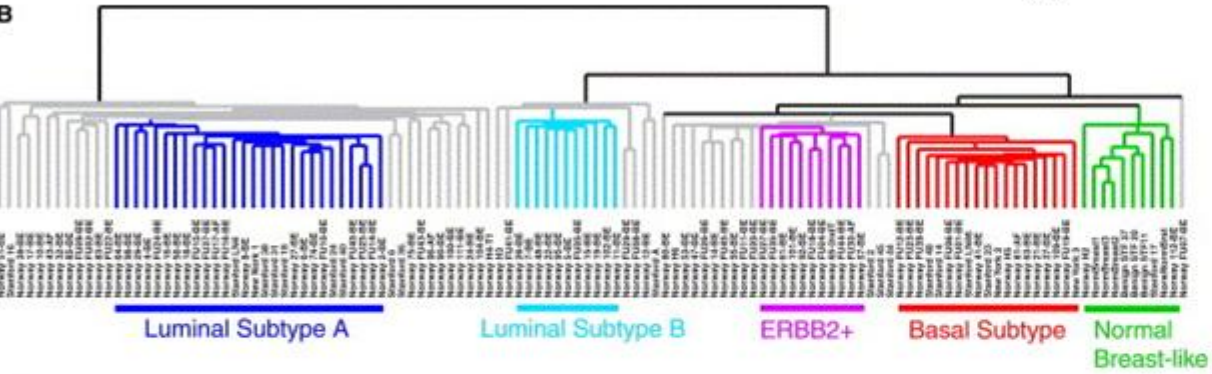
Perou, PNAS 1999 - Sorlie, PNAS 2001, 2003

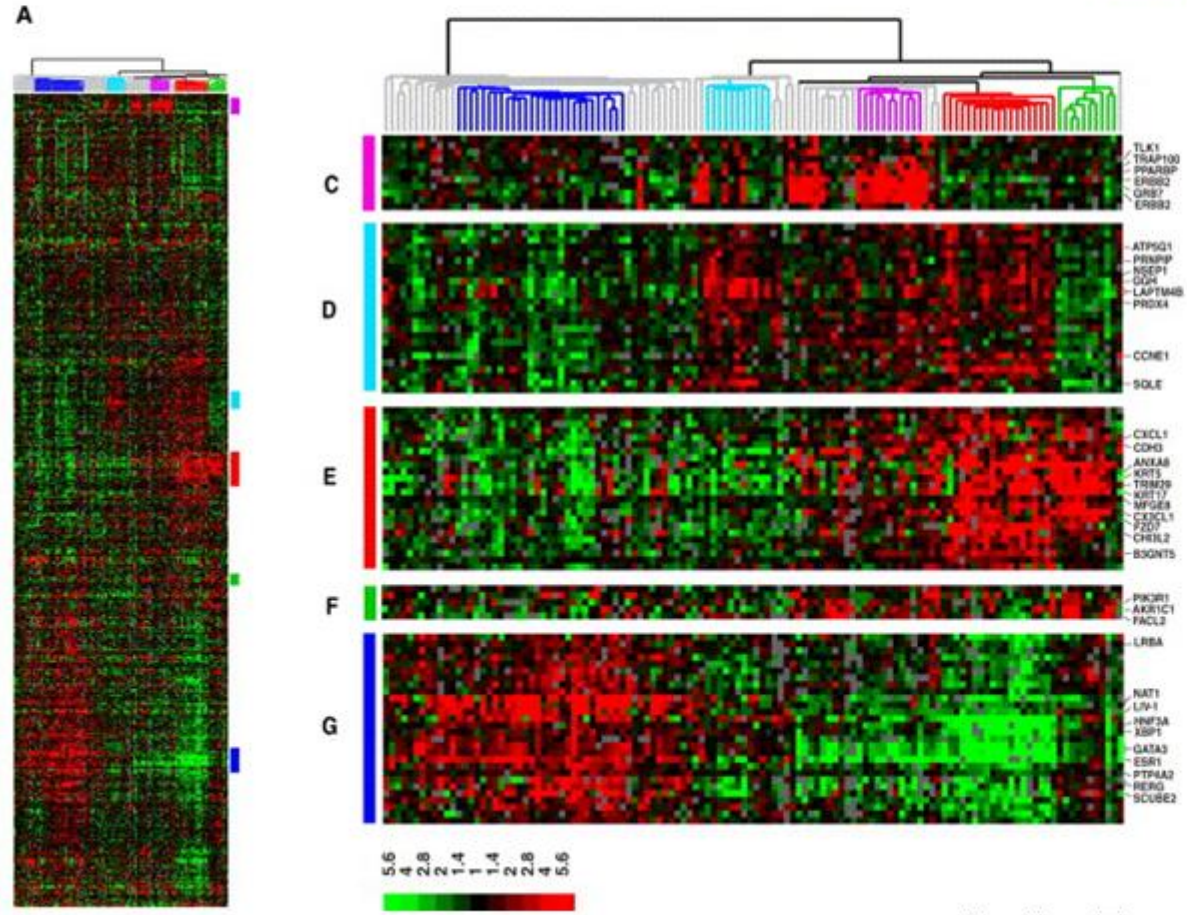


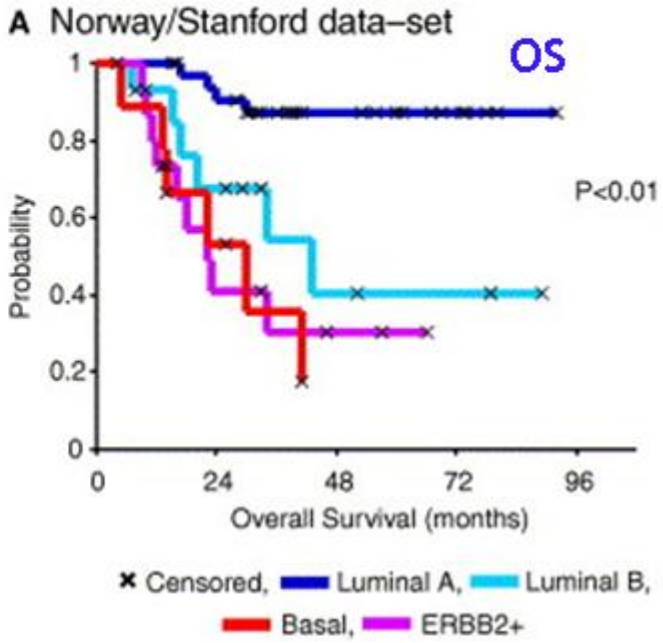
Bottom up : hypothèse biologique de départ

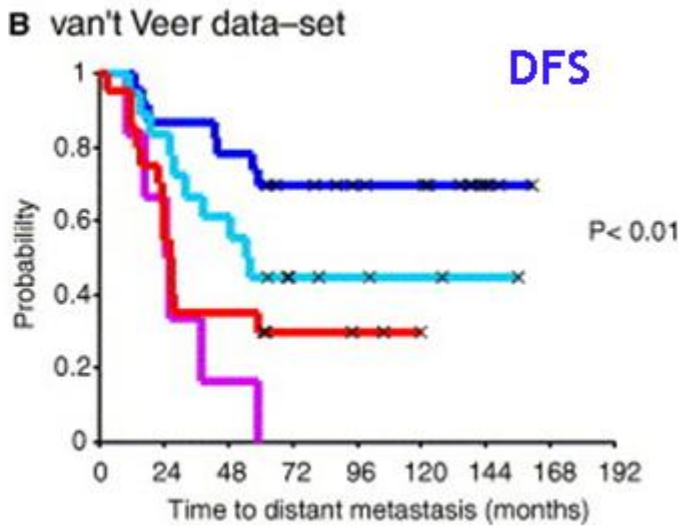
Top down : sans *a priori*

Breast Cancer is an Heterogeneous Group of Diseases



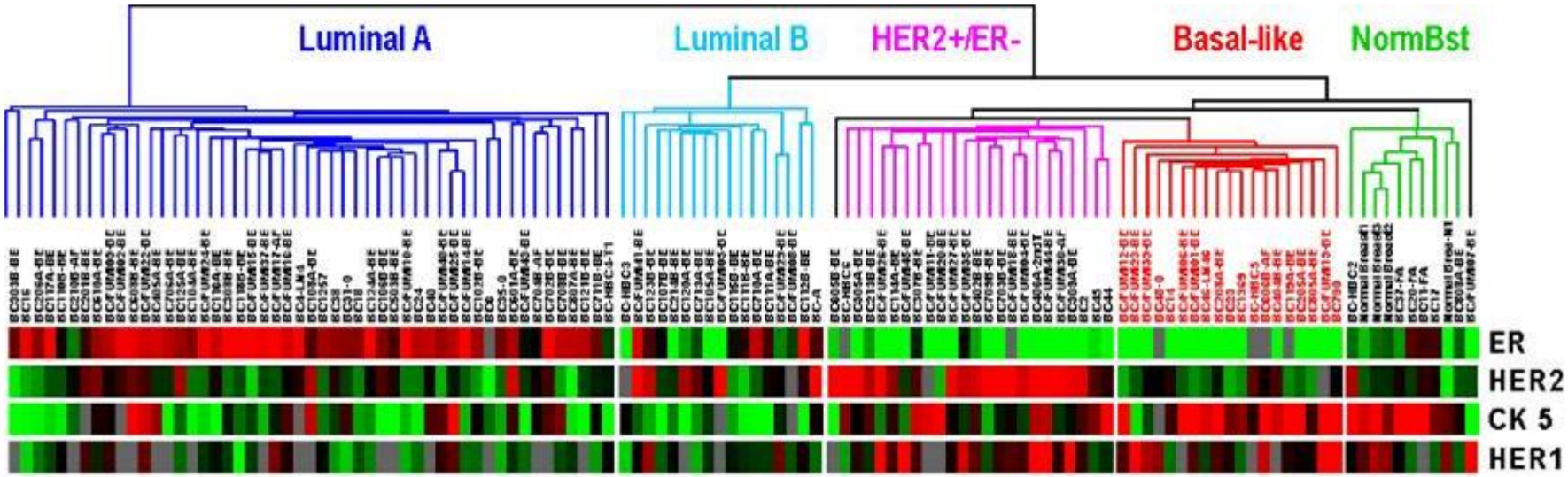






Sorlie, T et al: PNAS 2001; 98:10869-10874

T.O. Nielsen *et al.*, Clinical Cancer Research 10, 5367-74 (2004).



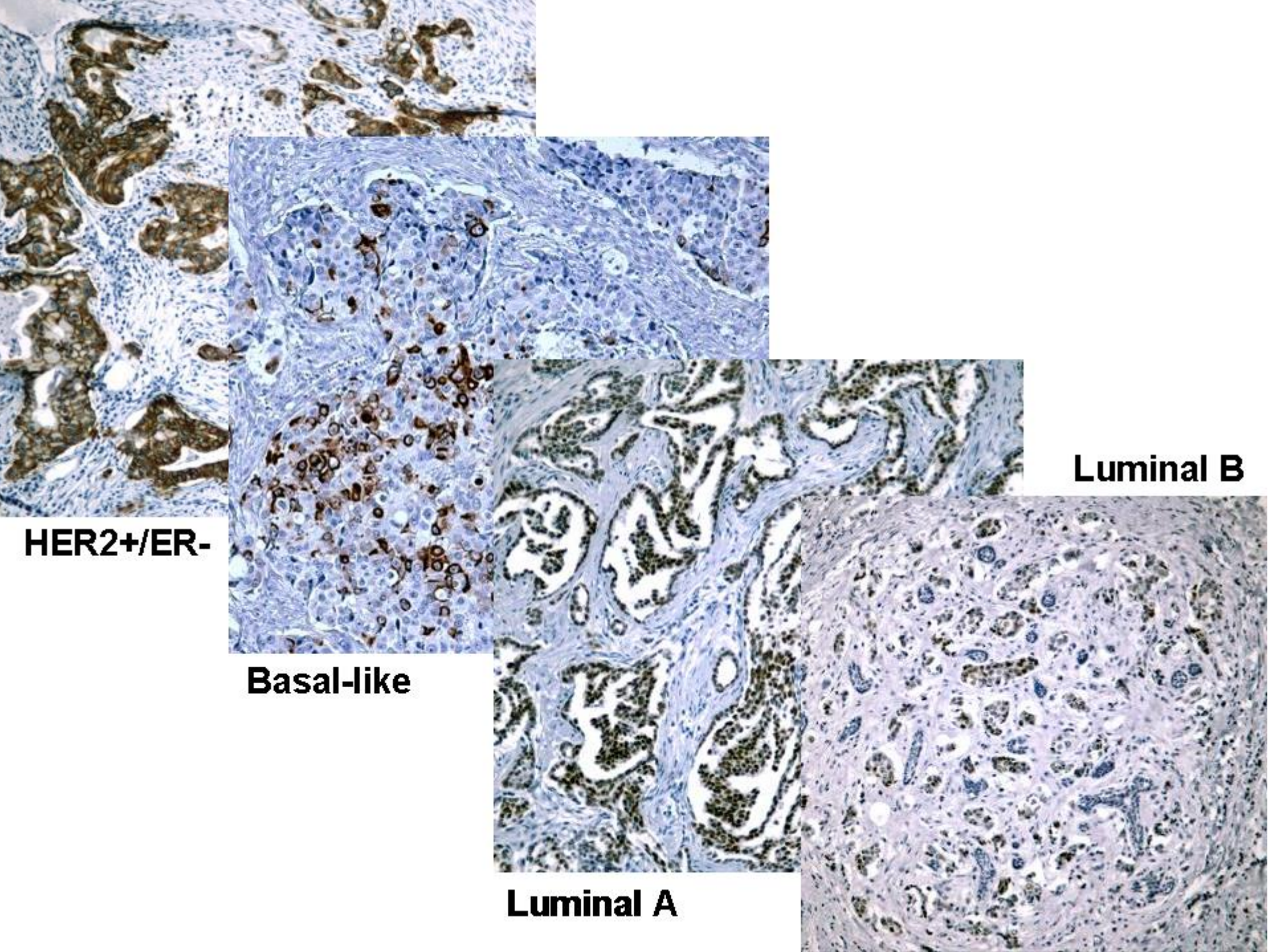
IHC intrinsic subtype surrogates

Luminal = ER+ and HER2-

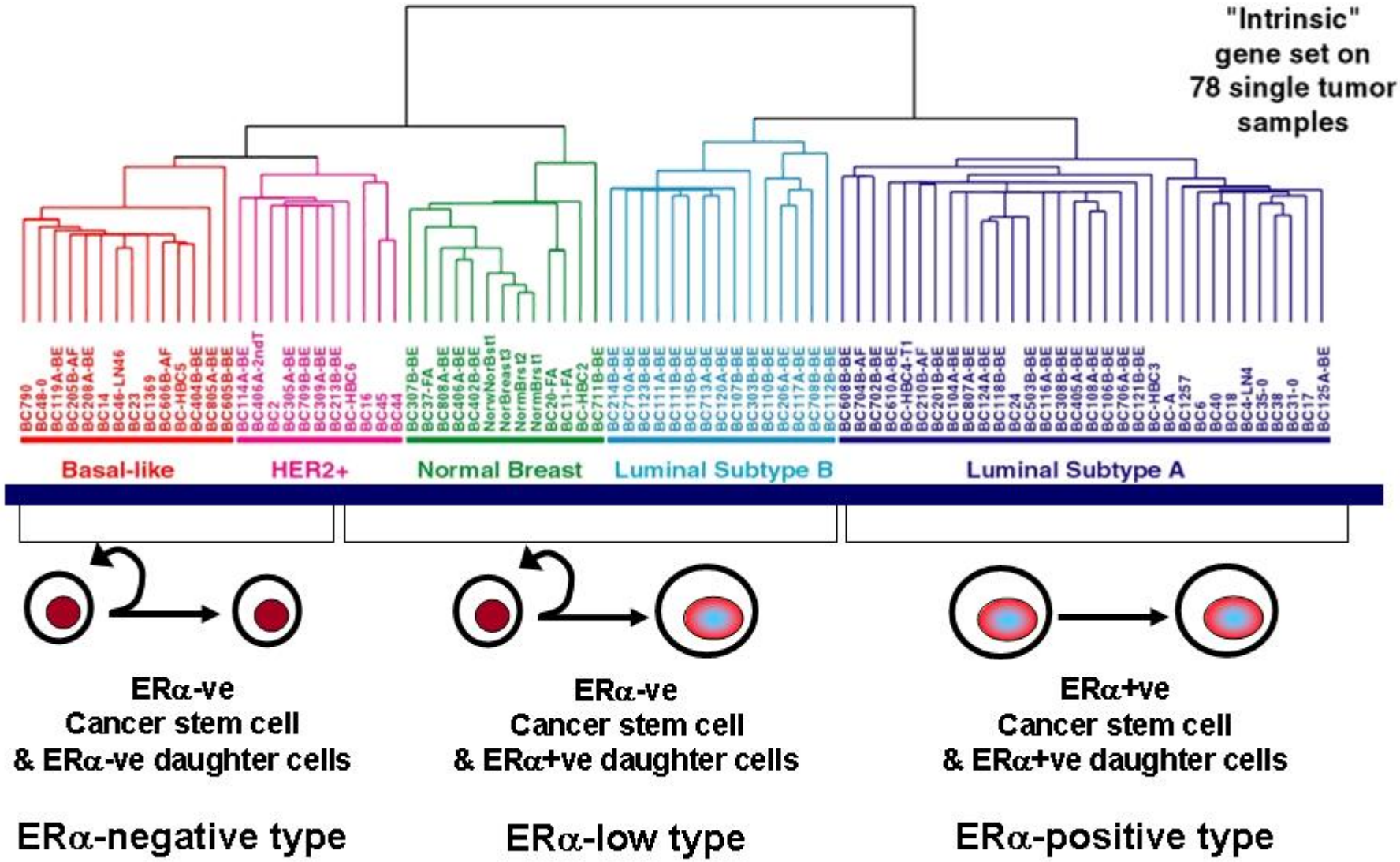
HER2+ = ER- or ER+ and HER2+ (3+)

Basal-like = ER-, HER2-, CK5/6+ and/or HER1+

Unclassified = negative for all 4 markers


HER2+/ER-
Basal-like
Luminal A
Luminal B

Breast cancer subtypes



ERα-ve
Cancer stem cell
& ERα-ve daughter cells

ERα-negative type

ERα-ve
Cancer stem cell
& ERα+ve daughter cells

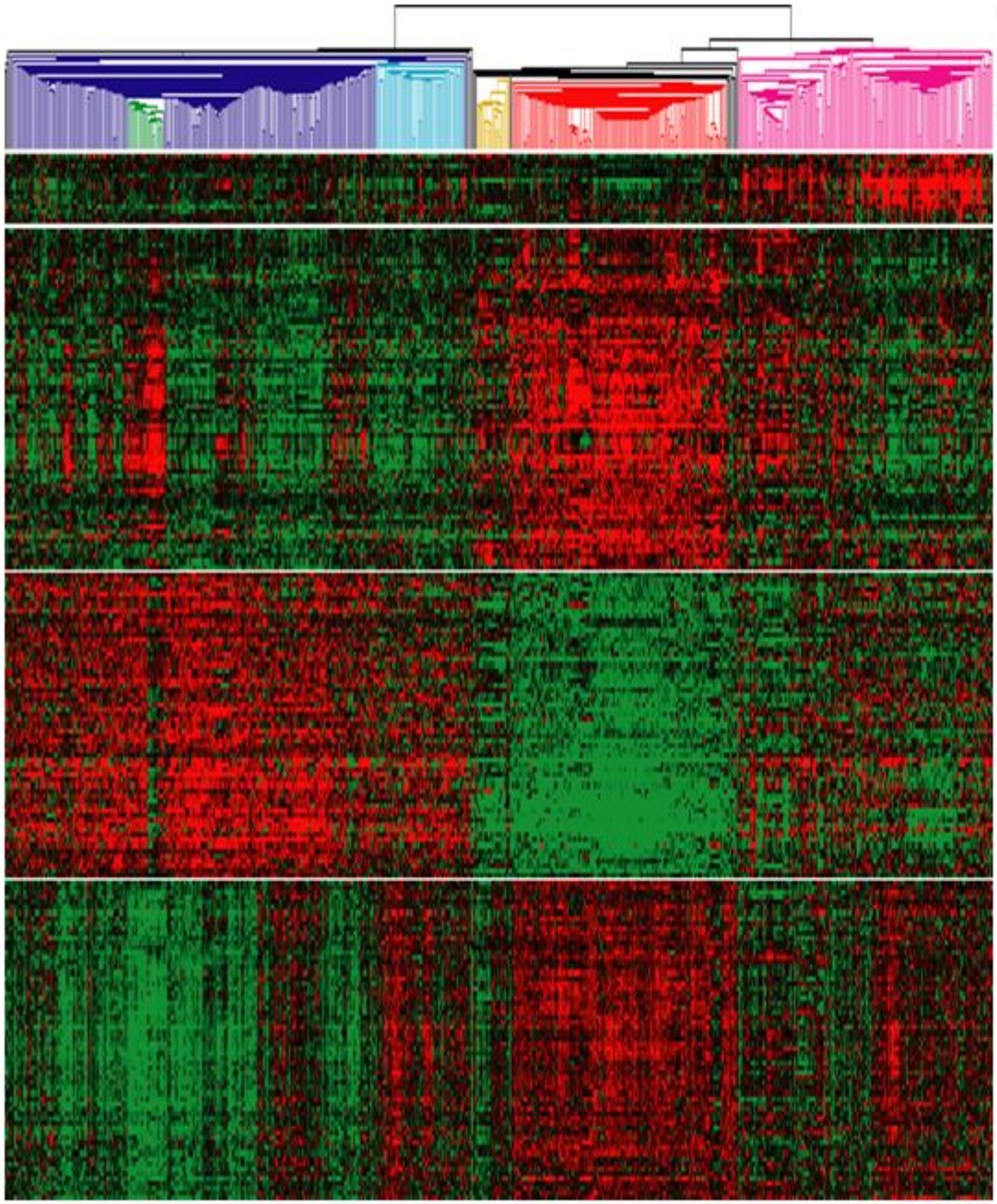
ERα-low type

ERα+ve
Cancer stem cell
& ERα+ve daughter cells

ERα-positive type

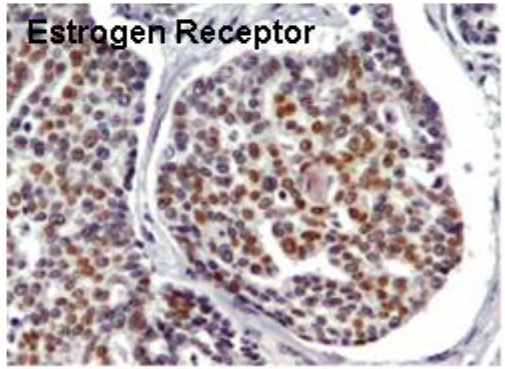
Clinical implications

- 2 families of ER+ breast cancer
- Basal-like breast cancer
- 4 families of HER2+ breast cancer

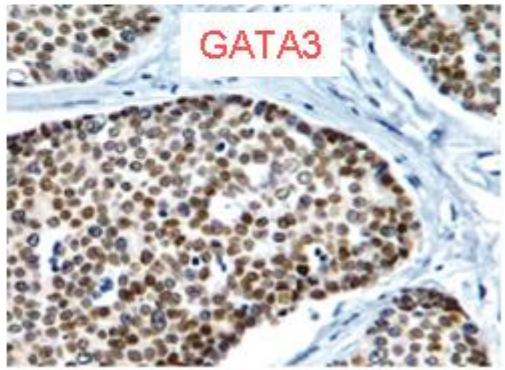


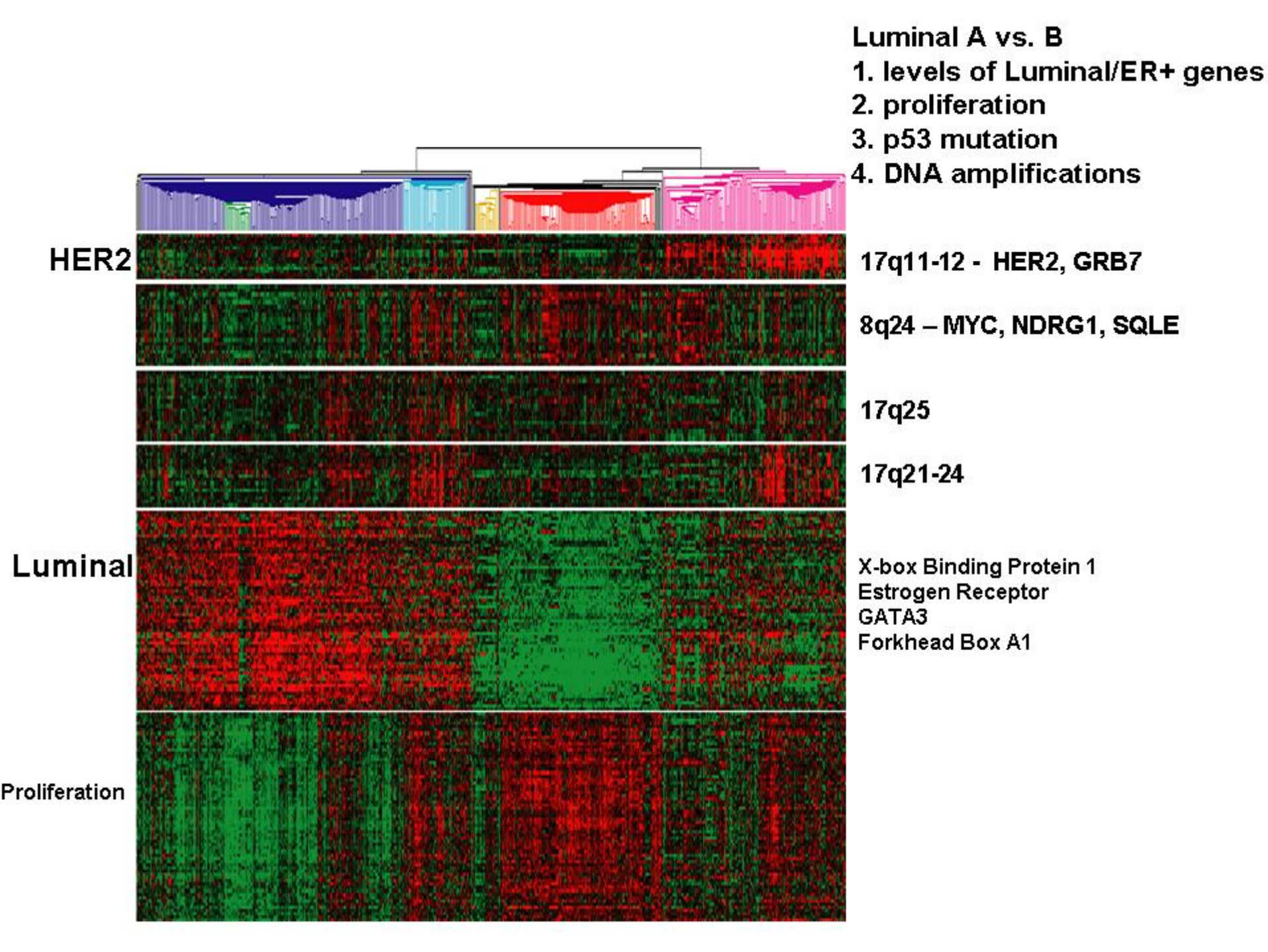
Luminal A and B (ER+)

1. continuum or distinct cells?
2. prognostic/predictive
3. ER-GATA3-FOXA1-XBP1
4. Cyclin D1 and BCL2

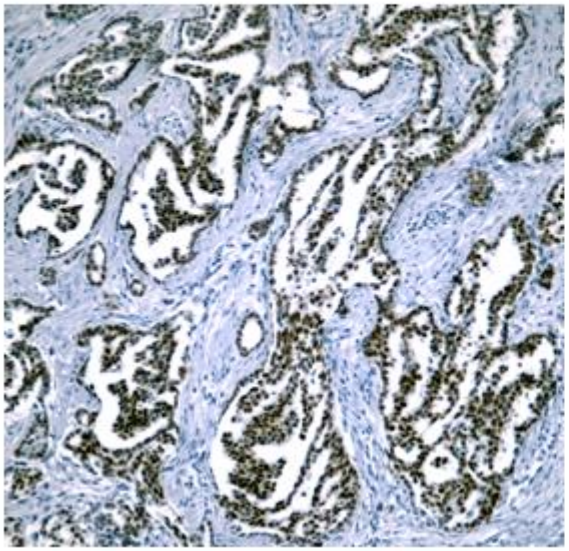


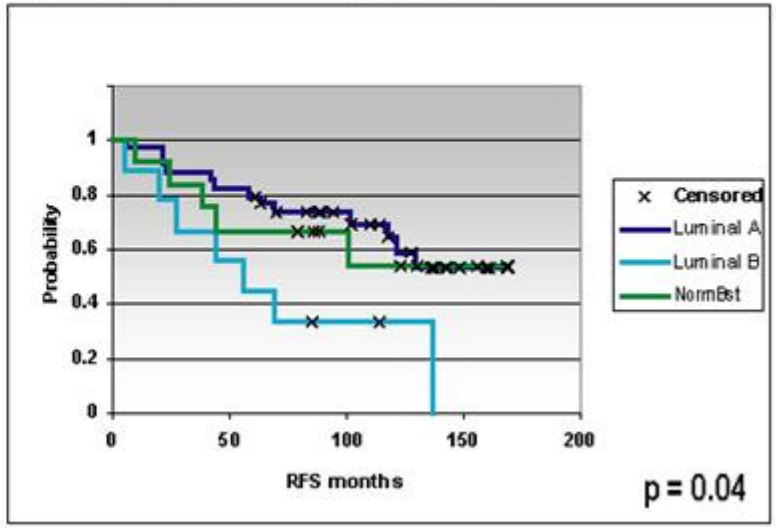
X-box Binding Protein 1
Estrogen Receptor
GATA3
Forkhead Box A1

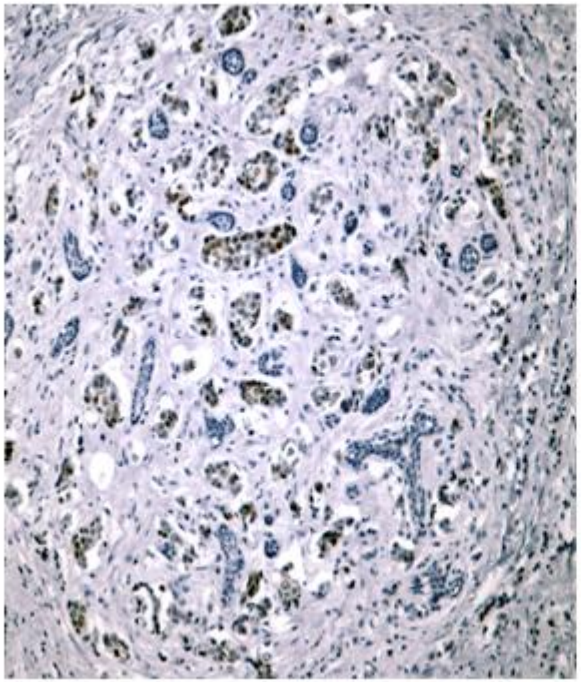


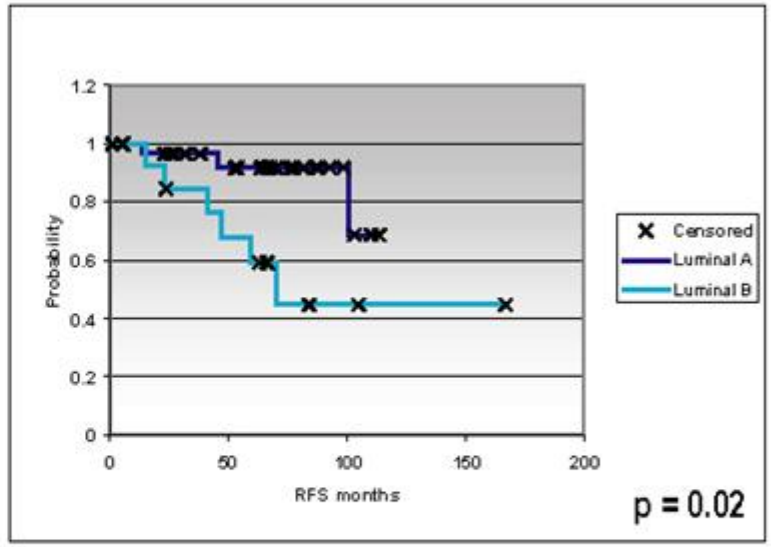

Luminal A vs. B
1. levels of Luminal/ER+ genes
2. proliferation
3. p53 mutation
4. DNA amplifications
HER2
17q11-12 - HER2, GRB7
8q24 – MYC, NDRG1, SQLE
17q25
17q21-24
Luminal
X-box Binding Protein 1
Estrogen Receptor
GATA3
Forkhead Box A1
Proliferation

60 Sample ER+ Tamoxifen-Treated Test Set
Ma et al., Cancer Cell 5, 1-10 (2004).





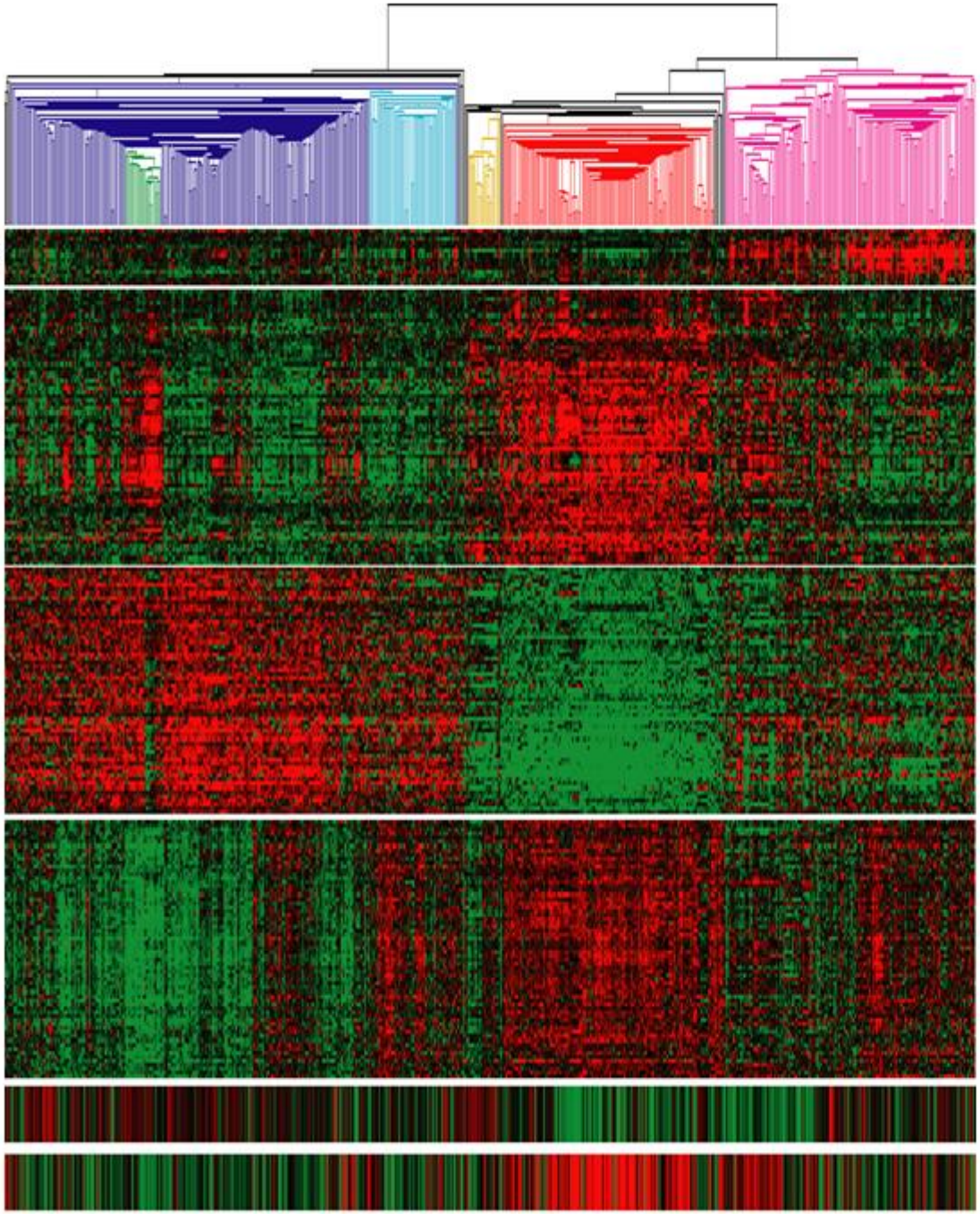




45 Tamoxifen Treated Test Set #2
Chang et al., PNAS 102, 3738-43 (2005) + UNC

Clinical implications

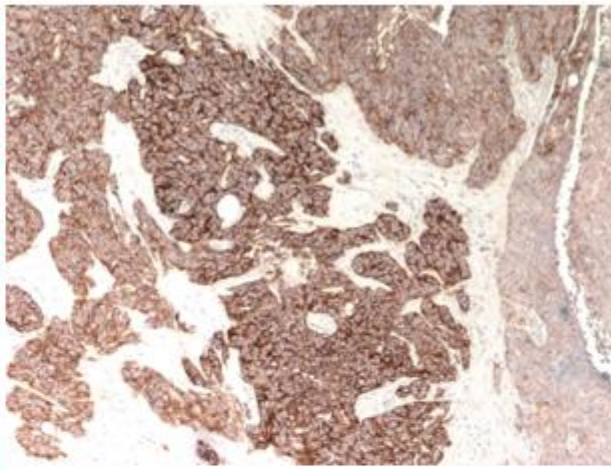
- 2 families of ER+ breast cancer
- Basal-like breast cancer
- 4 families of HER2+ breast cancer



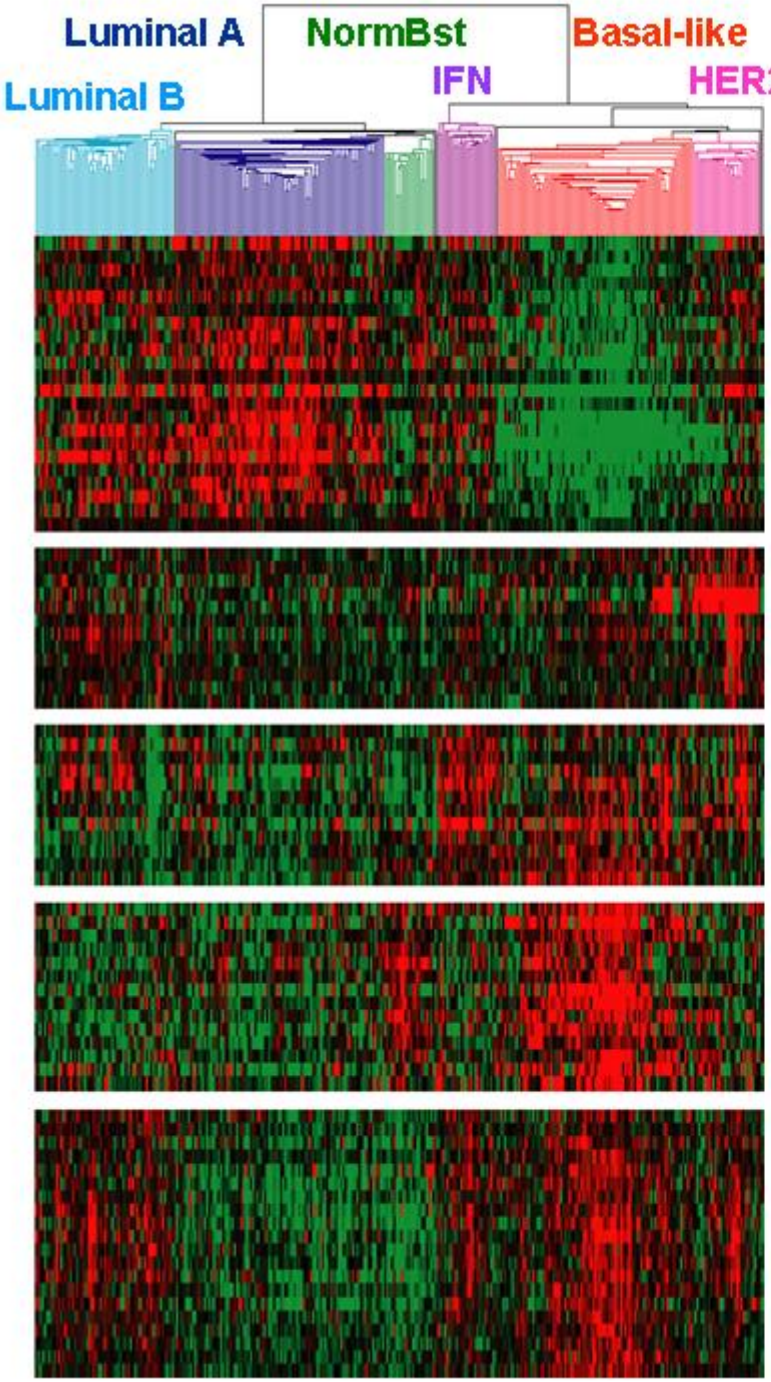
Basal-like subtype

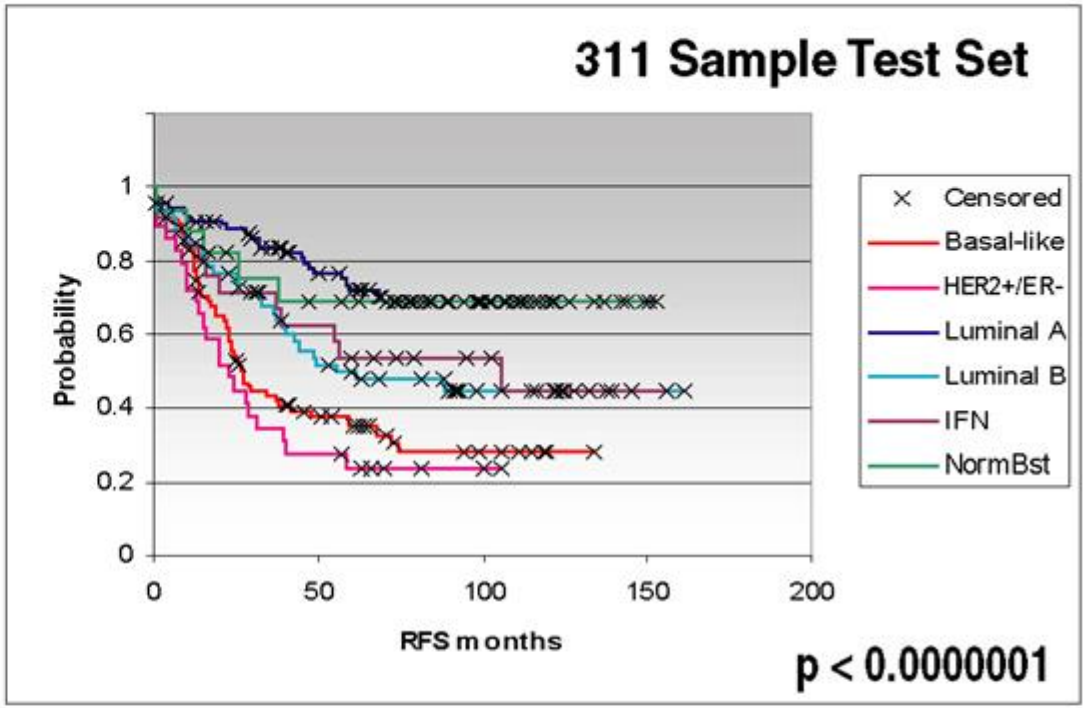
1. 10-20% of tumors
2. distinct cell type
3. BRCA1 carriers
4. 50% are p53 mutant
5. very proliferative

CRYAB
TCF4
Frizzled 7
LY6D
c-KIT
Keratin 5
Keratin 17



EGFR



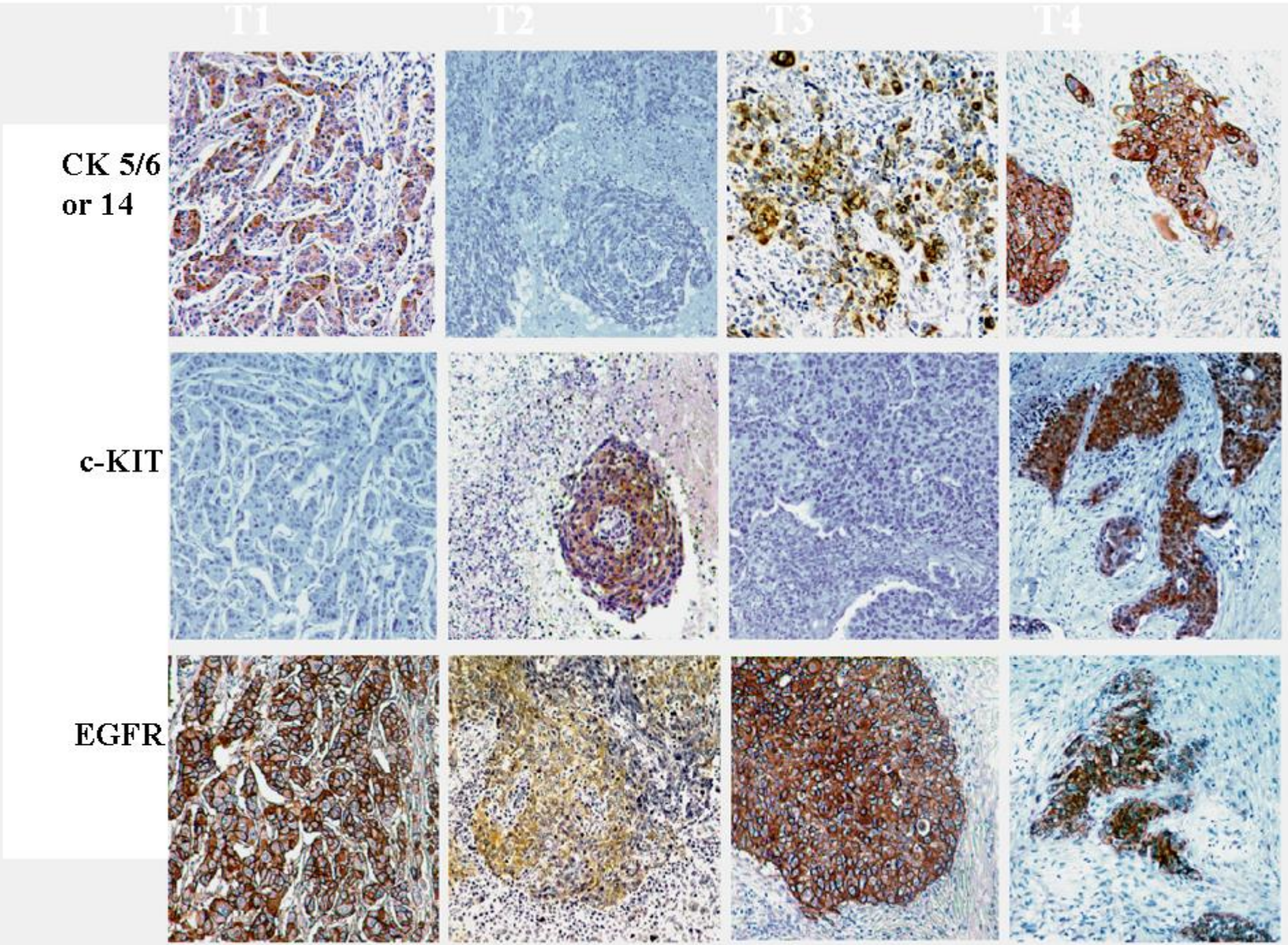


Poor prognosis of the basal-like group found in almost all the series so far published

Basal epithelial phenotype of breast cancer

- 3-15% of breast cancer
- Triple null phenotype: ER-, PR-, HER2- can be basal type BC
- Basal type signature: ER-, HER2-, EGFR+, CK14 + (or CK5-6 +)
- Other markers: osteonectin, CK17, SMA, GFAP, calponin

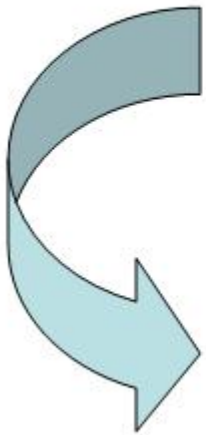
Foulkes JNCI 2003


T1
T2
T3
T4
CK 5/6
or 14
c-KIT
EGFR

BRCA1 BREAST CANCER

Basal epithelial phenotype

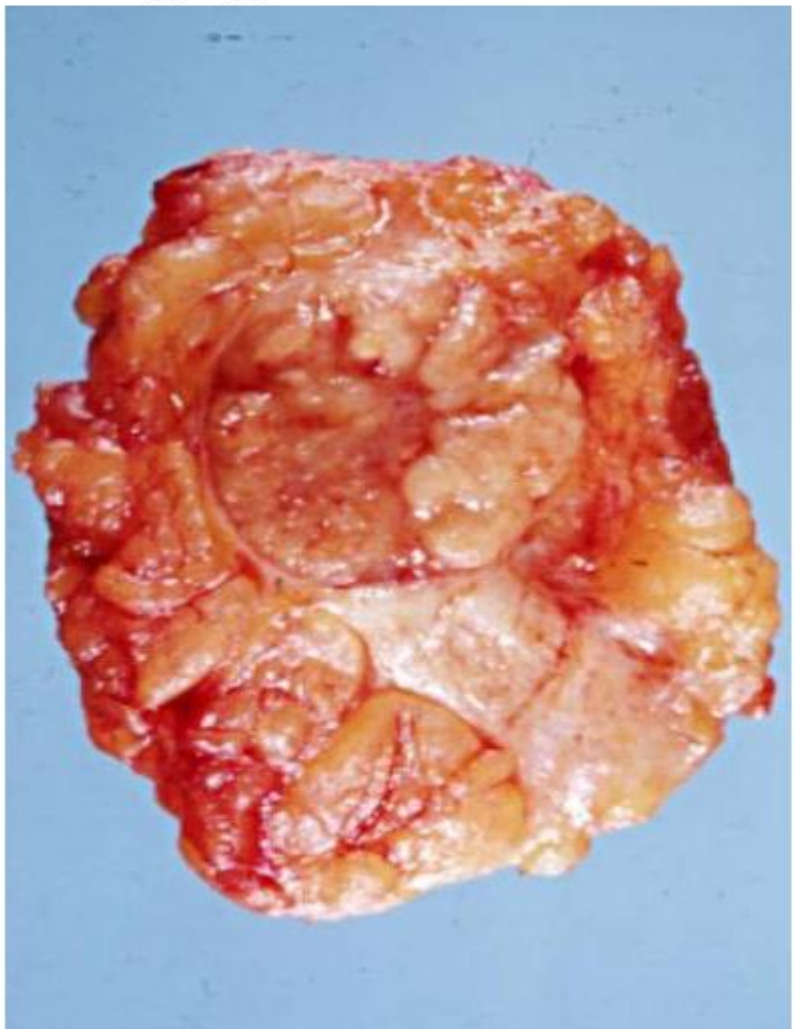
- Morphologic features
  - High grade
  - Necrosis
  - Atypical medullary phenotype
  - TP53 mutations

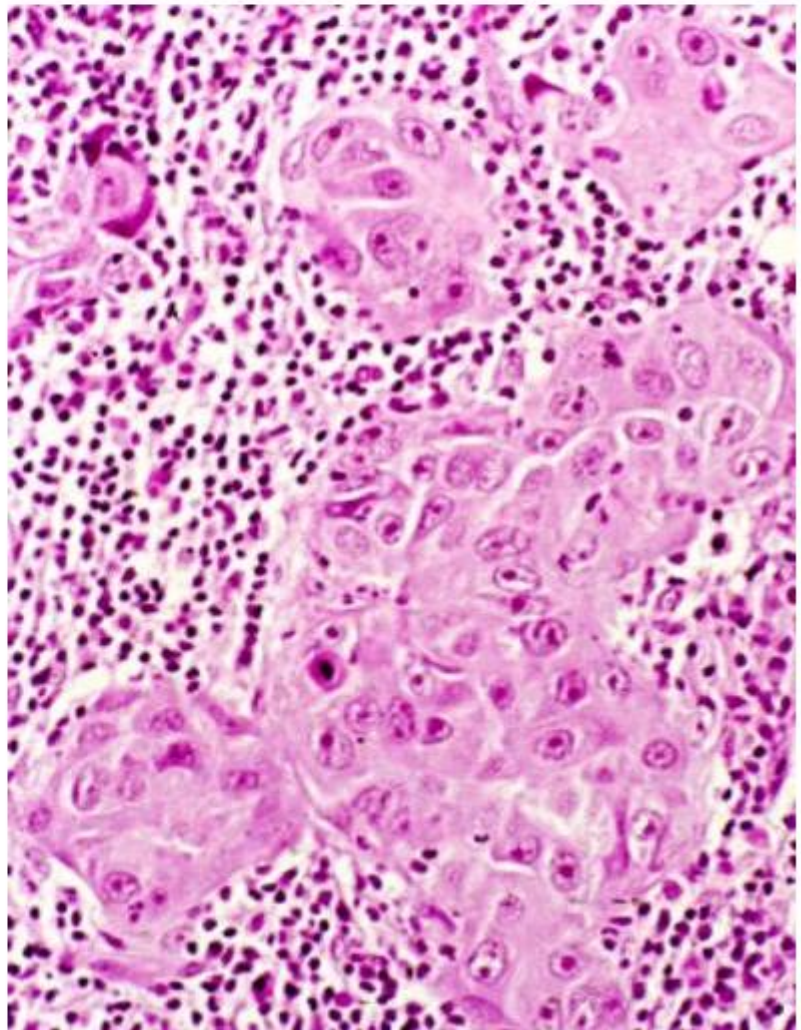


Similar to BRCA1 associated breast tumors

Pathology of familial breast cancer

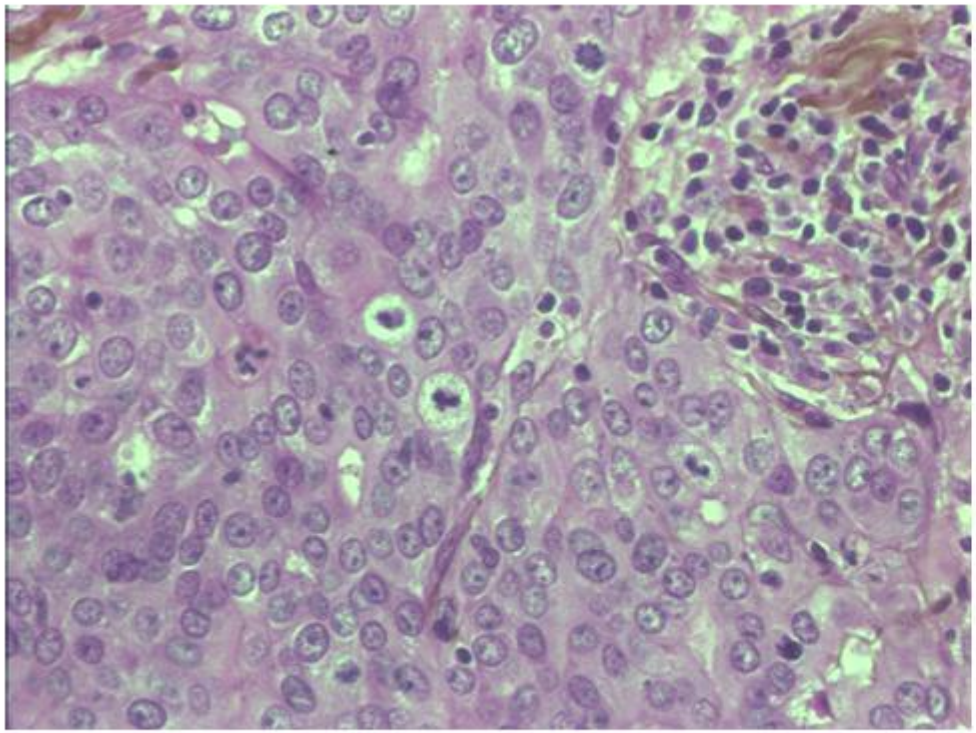
High grade Invasive ductal carcinoma or "medullary like"





Data from the Breast Cancer Linkage Consortium Study

- Tumors linked to BRCA1



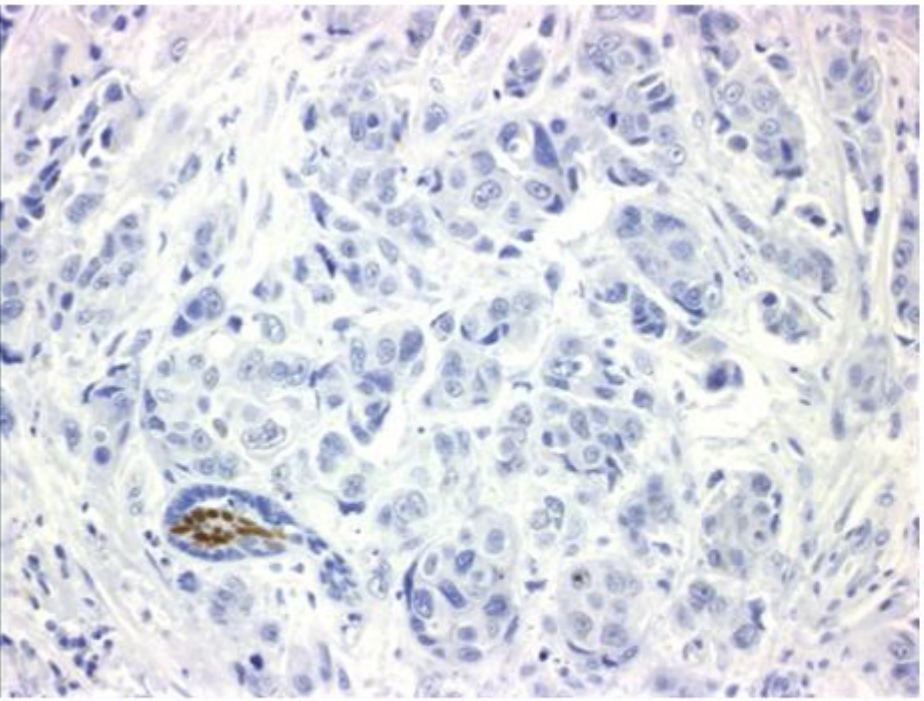
Lakhani Lancet 1997, JNCI 1998

Multivariate analysis

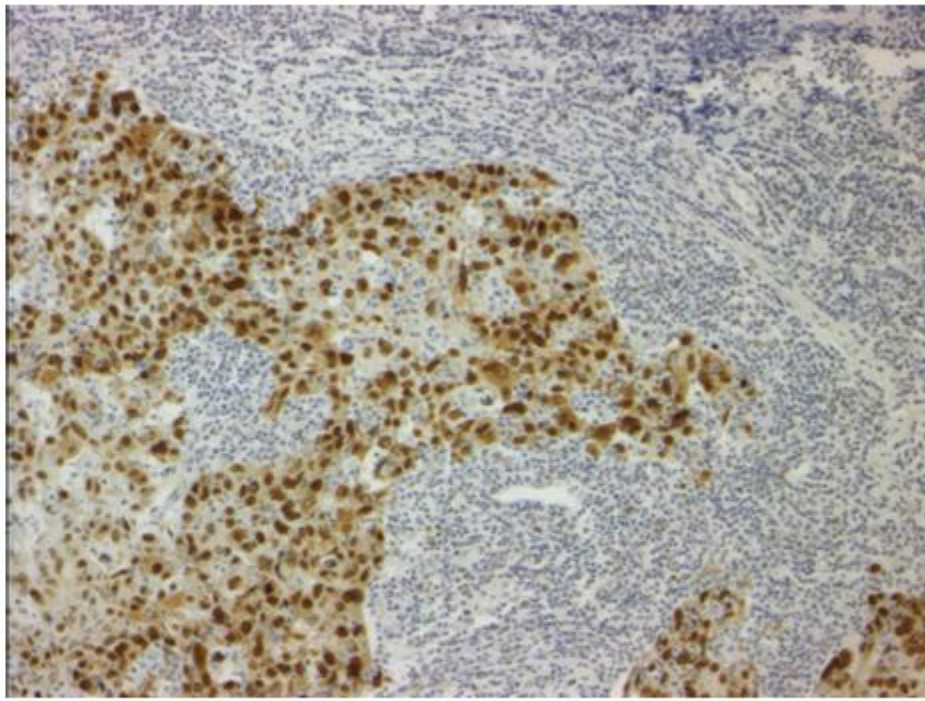
- High mitotic grade
- Good limitation
- Lymphoplasmocytic infiltration

BRCA1 IHC PROFILE

ER NEGATIF



P53 POSITIVE



Lakhani JCO 2002

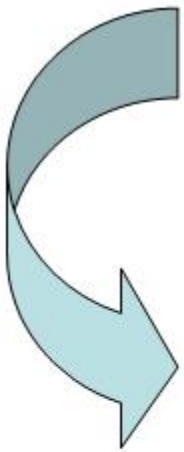
Familial Breast Cancer

- BRCA 1 Prediction
- BRCA 1 – prevalence <60yrs = 2.0%
  - –Er +ve 0.4%
  - –ER –ve, ck –ve 1.6%
  - –ER-ve, ck14 +ve 5.2%
  - –ER –ve, ck 5/6 +ve 10.1%
  - –ER –ve, ck 5/6 +ve, ck 14 +ve 55%

Lakhani Clin Cancer Res 2005 11 5175

« Expression signatures »

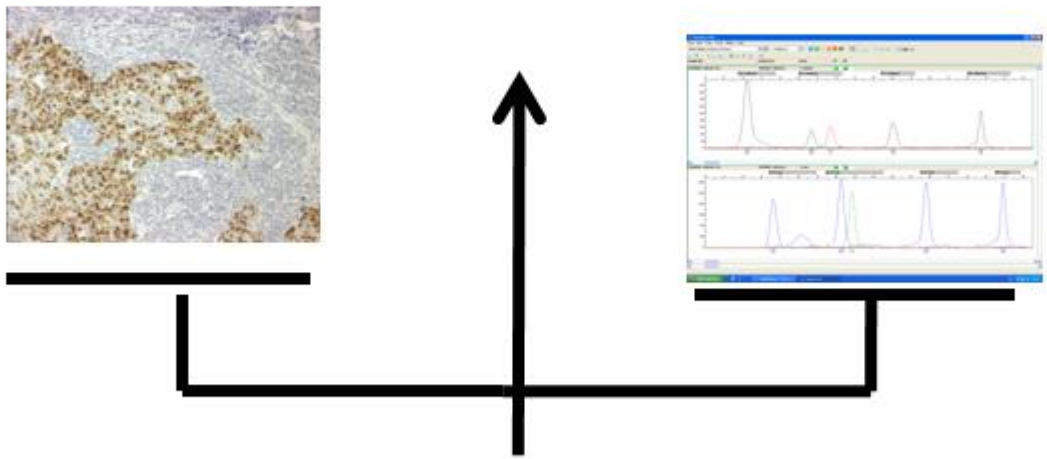
BRCA 1 and 2 mutated have a different profile and could be distinguished from sporadic breast cancer (Hedenfalk, *New Engl J Med 2001*)



This profile could be used instead of sequencing BRCA genes

HISTOPATHOLOGICAL FEATURES

- Cost effective tool for genetic screening



Data from the Breast Cancer Linkage Consortium Study

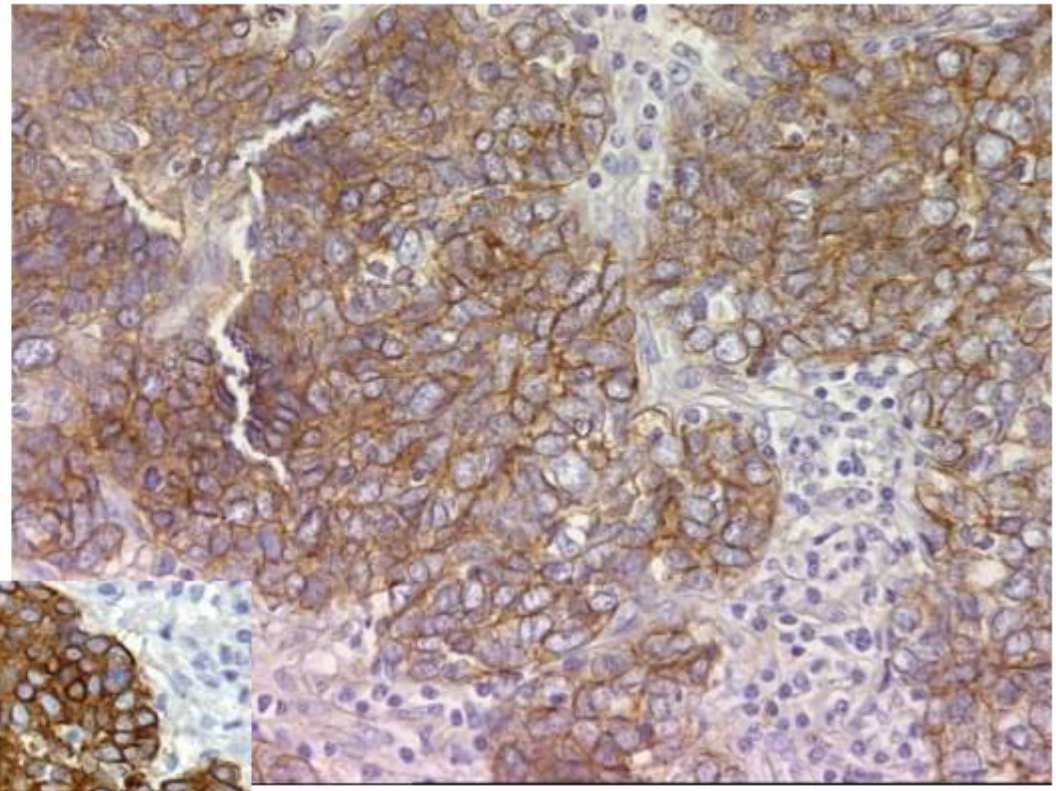
Lakhani, Clin Cancer Res 2005

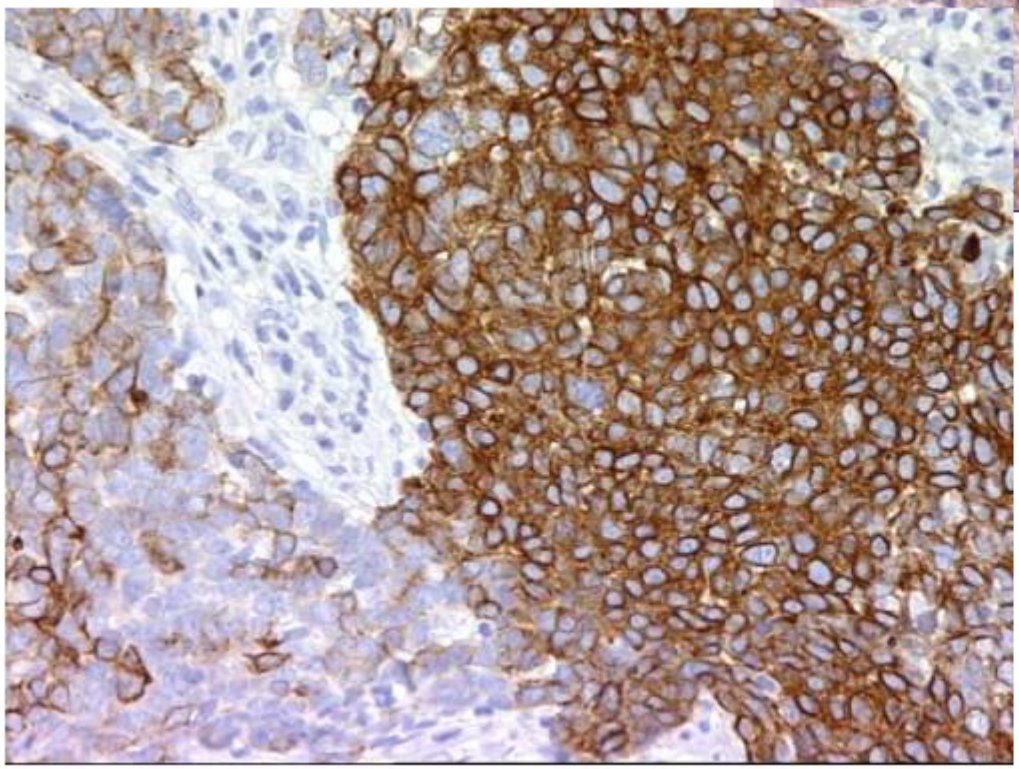
- 182 BRCA1 tumors, 63 BRCA2, 109 controls
- CK14, CK5/6,CK17, EGFR, Osteonectin

Lakhani: Clin Cancer Res 2005
Basal phenotype and familial breast cancer

IHC	Controls n = 109	BRCA1 n = 182
CK14 +	11.8%	**60.6%** **p<0.0001**
CK5/6 +	6.6%	**57.6%** **p<0.0001**
CK17 +	9.6%	**53.3%** **<0.0001**
Osteonectin +	18.7%	**43.2%** **P=0.0001**
EGFR +	21.3%	**67.3%** **p<0.0001**

EGFR





CK5-6

Prevalence of combined phenotypes defined by ER, CK14 and CK5/6

ER	CK14	CK5/6	BRCA1%	Control %
Pos			9.6	67.2
Neg	Neg	Neg	20.9	24
Neg	Neg	Pos	13.4	2.4
Neg	Pos	Neg	12.4	4.8
Neg	Pos	Pos	43.8	1.6

Lakhani: Clin Cancer Res 2005

BRCA1 signature:
ER-, CK14+, CK5/6+

BRCA1 phenotype
(Albiges L Ann Oncol 2005)

	BRCA1	BRCA2	Non mutated	P (χ^2)
N	15	12	58	
Age	45.6	48	51.7	
ER+	35%	75%	79%	0.007
Bone mets	13%	58%	55%	0.01
Lung mets	60%	0%	38%	0.005
Brain mets	**67%**	**0%**	**10%**	**10^{-5}**

Basal-like cancer

- 25% of Grade III breast tumors (Fulford 2007)
- Higher prevalence in premenopausal african-american (39%) versus menopausal AA (14%) or non AA (16%) (Carey 2006)
- Classical phenotype: medullary like
- Heterogeneous group: myoepithelial differenciation, apocrine tumors, low grade tumors, with different gene expressions

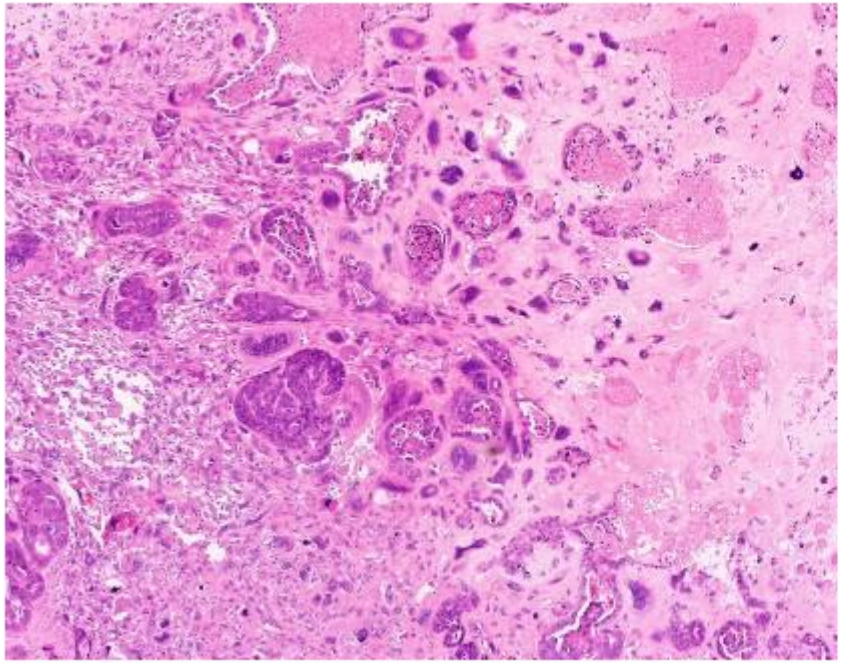
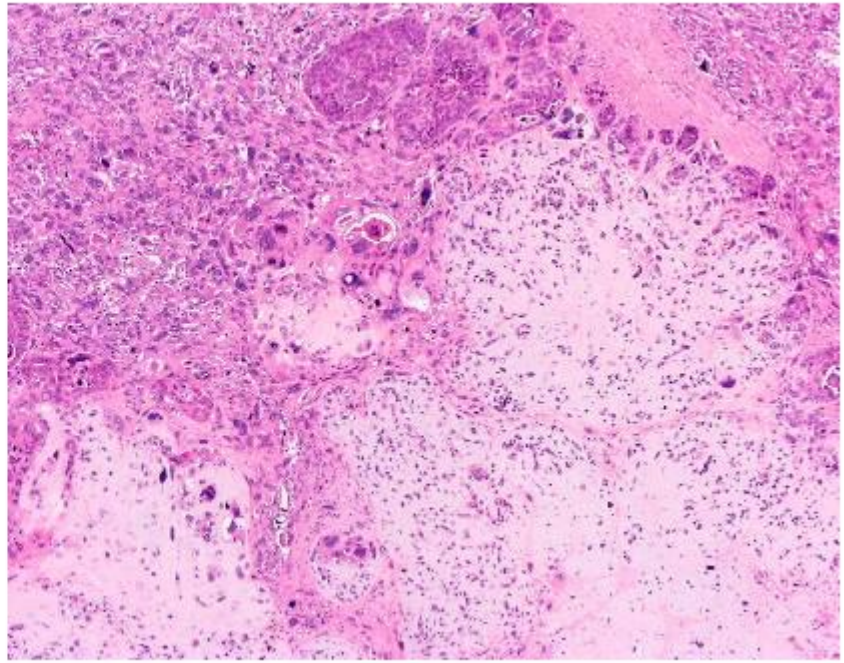
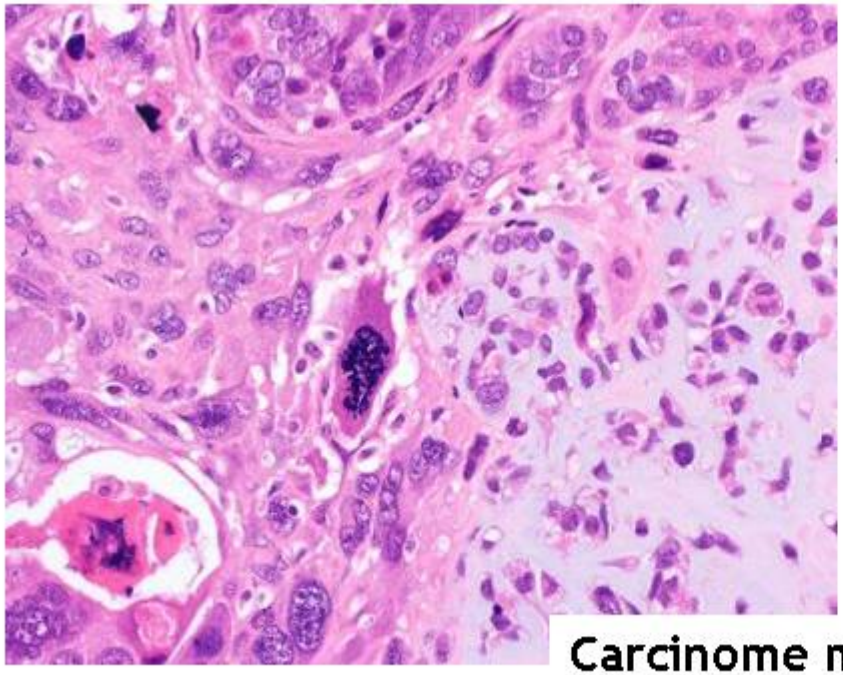
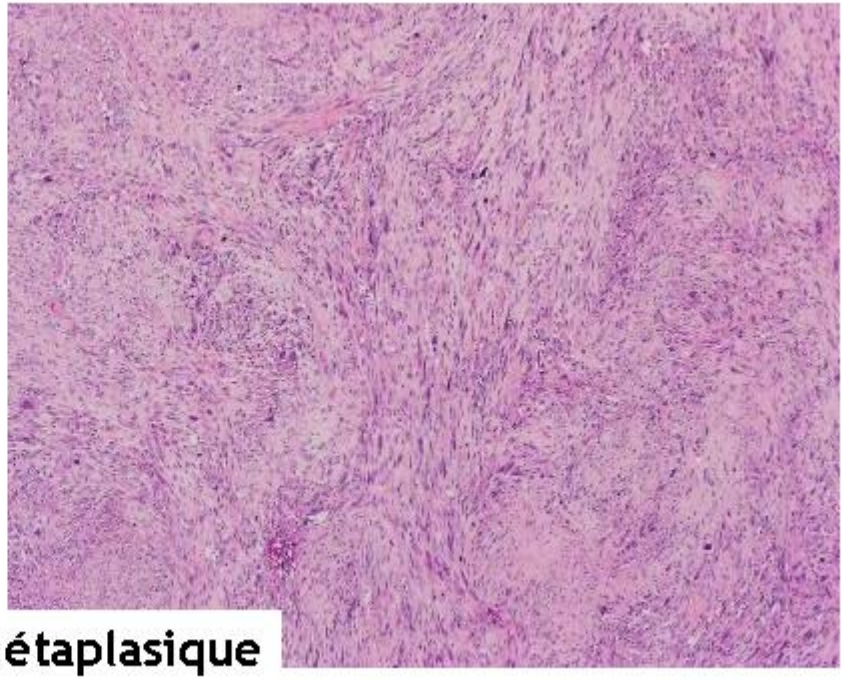
Better response to treatment for basal-like tumors

- *Rouzier R Clin Cancer Res 2005*
  - 82 IBC treated by neoadjuvant chemotherapy with paclitaxel followed by FAC
  - pCR
    - 45% for HER2+ and/or Basal-like cancer
    - 6% for luminal cancer
    - 0% for normal-like cancer
  - Different gene involved
- Sensitivity to CDDP

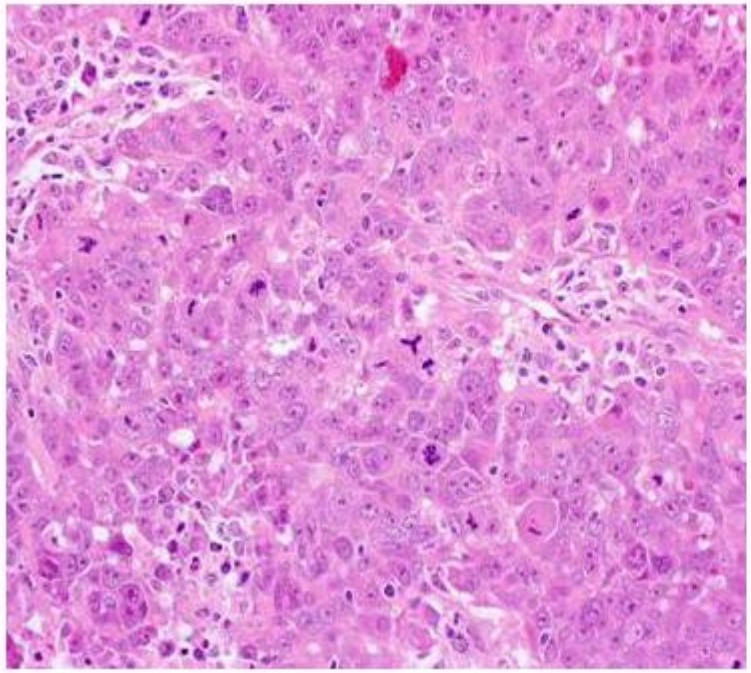
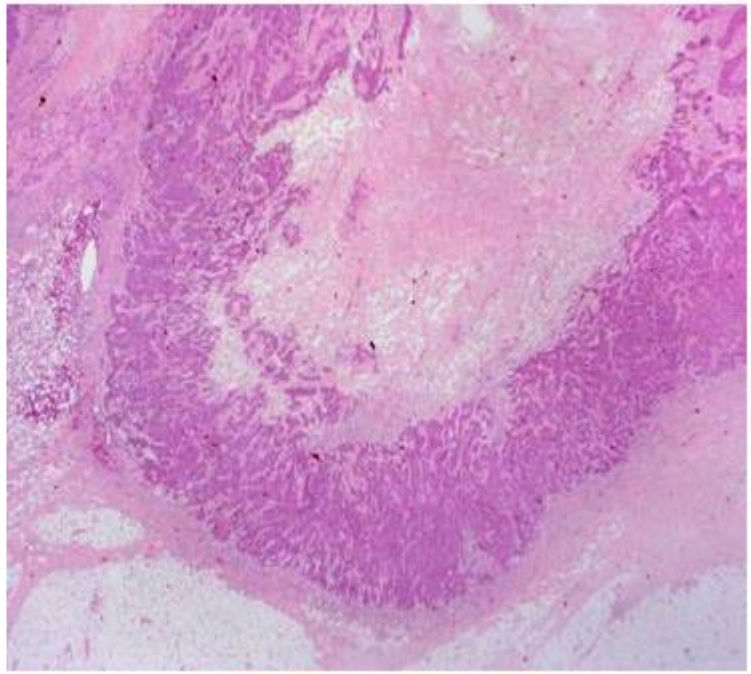
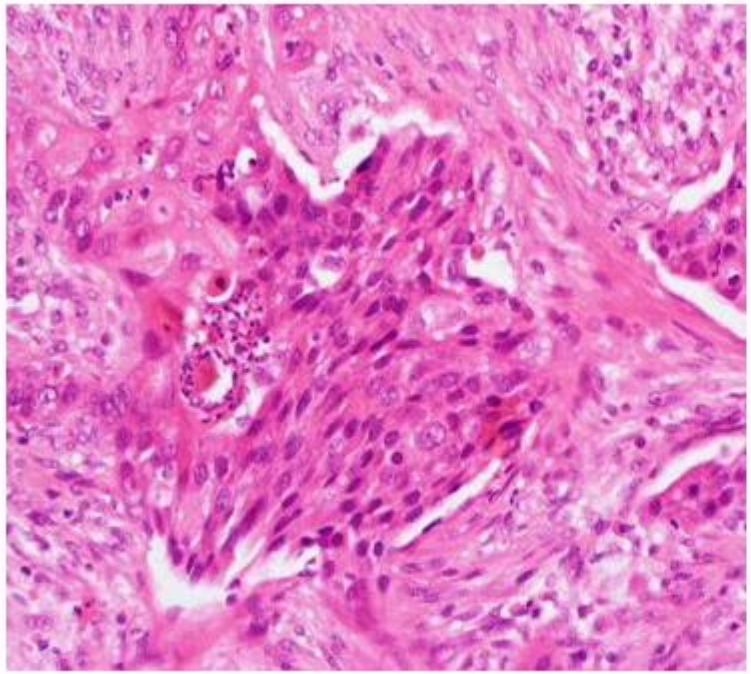
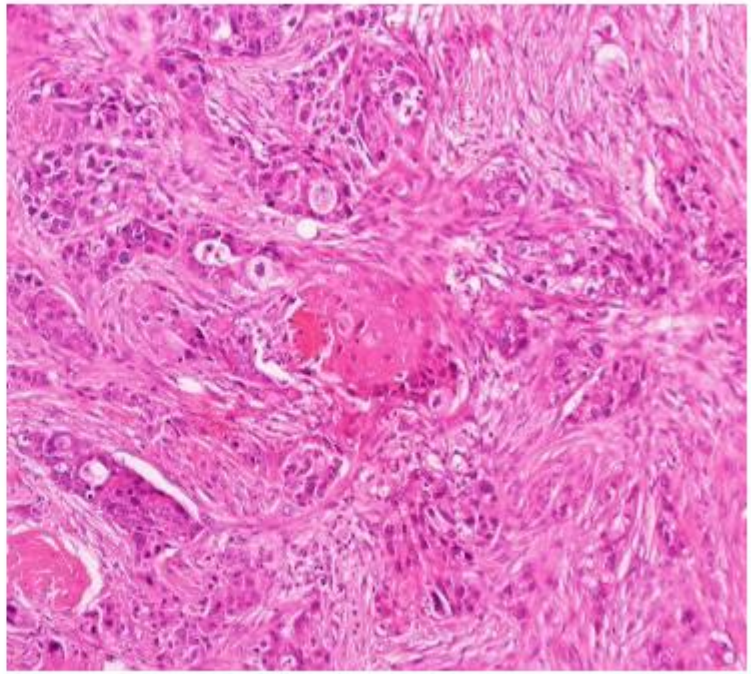
Histopathological subtypes

- Basal like group encompasses a large variety of of tumors (high grade IDC, special types like adenoid cystic carcinoma or low grade squamous carcinoma…) with distinct prognosis and predictive implications that escape molecular identification

So, we still have to histotype the tumors

Carcinome métaplasique

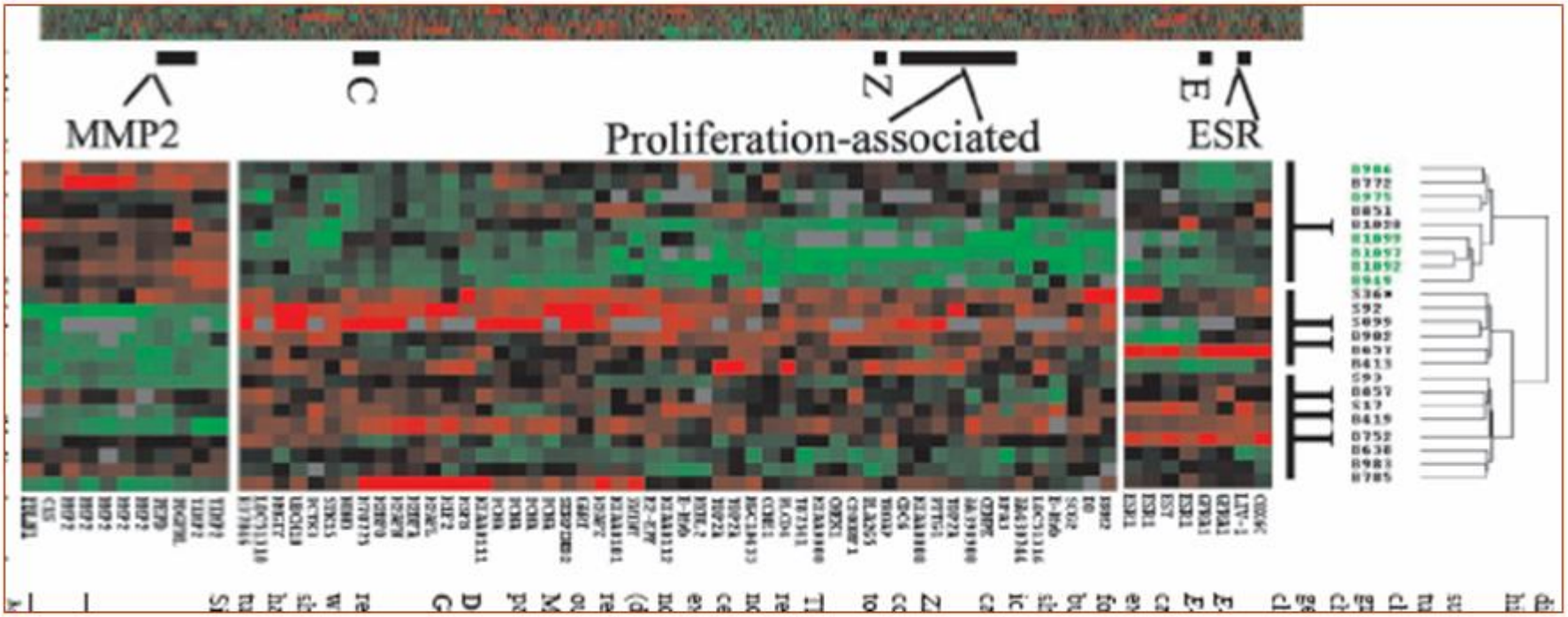
Histopathological subtypes

- Loss of 16q tumor suppressor gene ?
- Loss of expression of E cadherin ++++
- luminal A / normal like sub type
- Resistance to apoptose CIDEC , E cadherin ,BCL2
- hypoangiogenesis (Thrombospondin ++ / VEGF--)
- Lymphagenesis +++
- Pleiomorphic, solid, alveolar sub types: luminal B or HER2+

[CANCER RESEARCH 63, 7167–7175, November 1, 2003]

Differentiation of Lobular *versus* Ductal Breast Carcinomas by Expression Microarray Analysis[1]

James E. Korkola,[2] Sandy DeVries, Jane Fridlyand, E. Shelley Hwang, Anne L. H. Estep, Yunn-Yi Chen, Karen L. Chew, Shanaz H. Dairkee, Ronald M. Jensen, and Frederic M. Waldman



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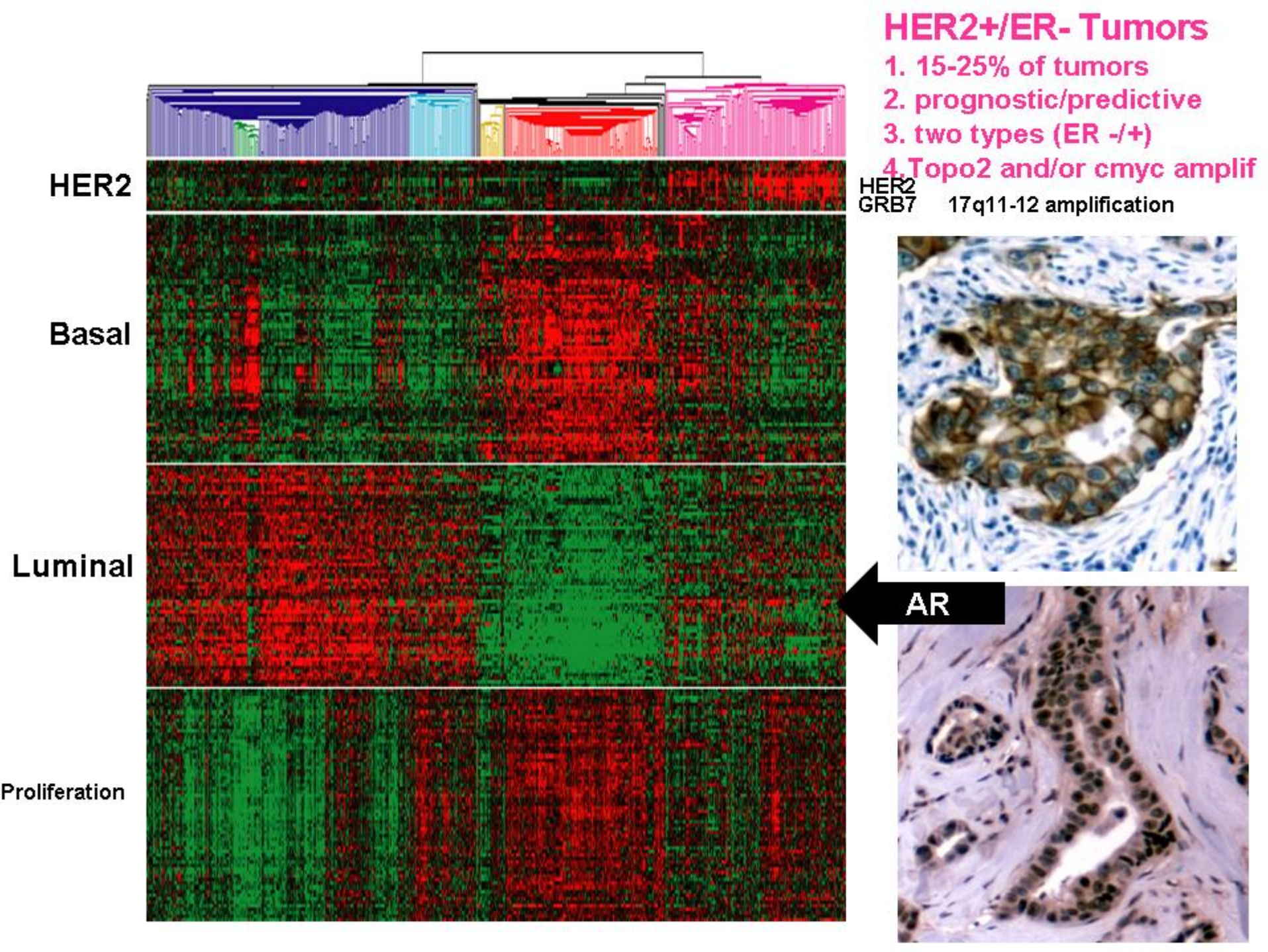
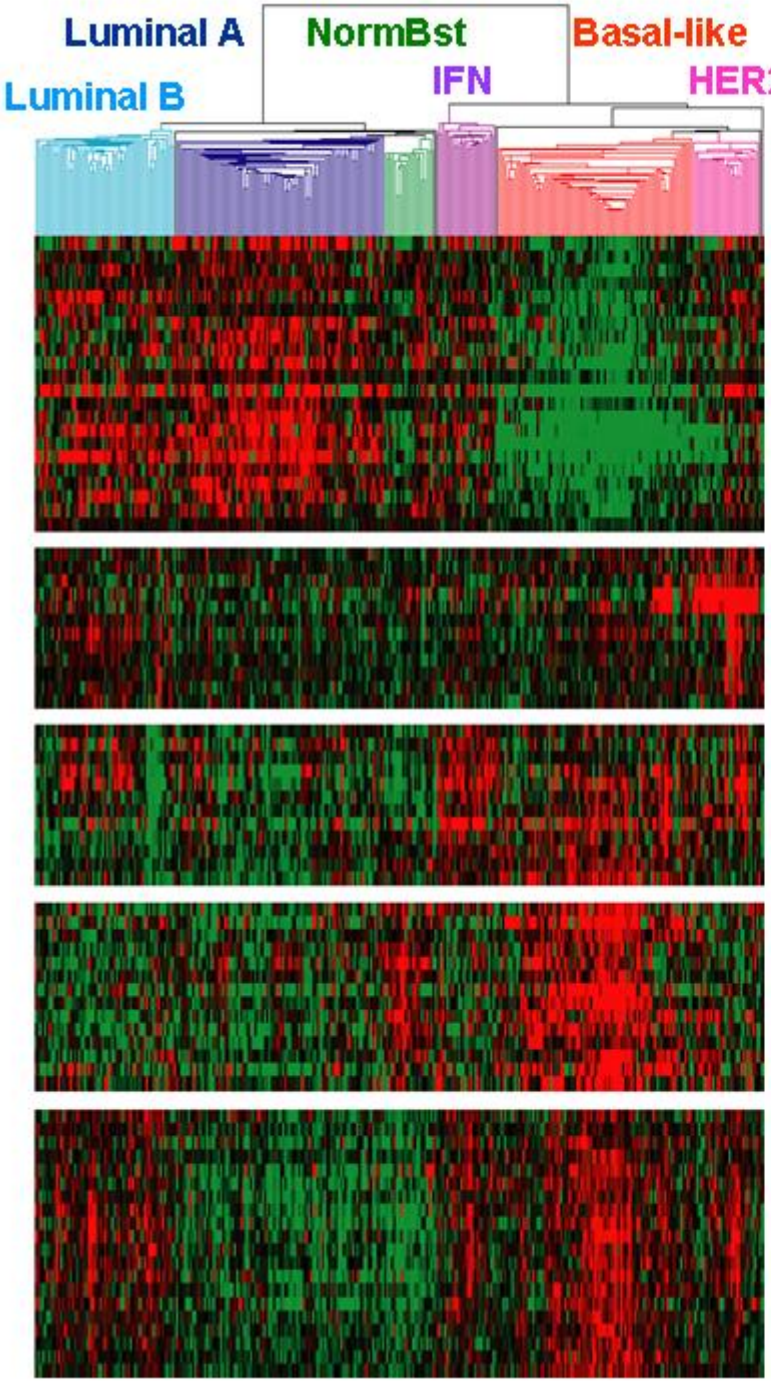
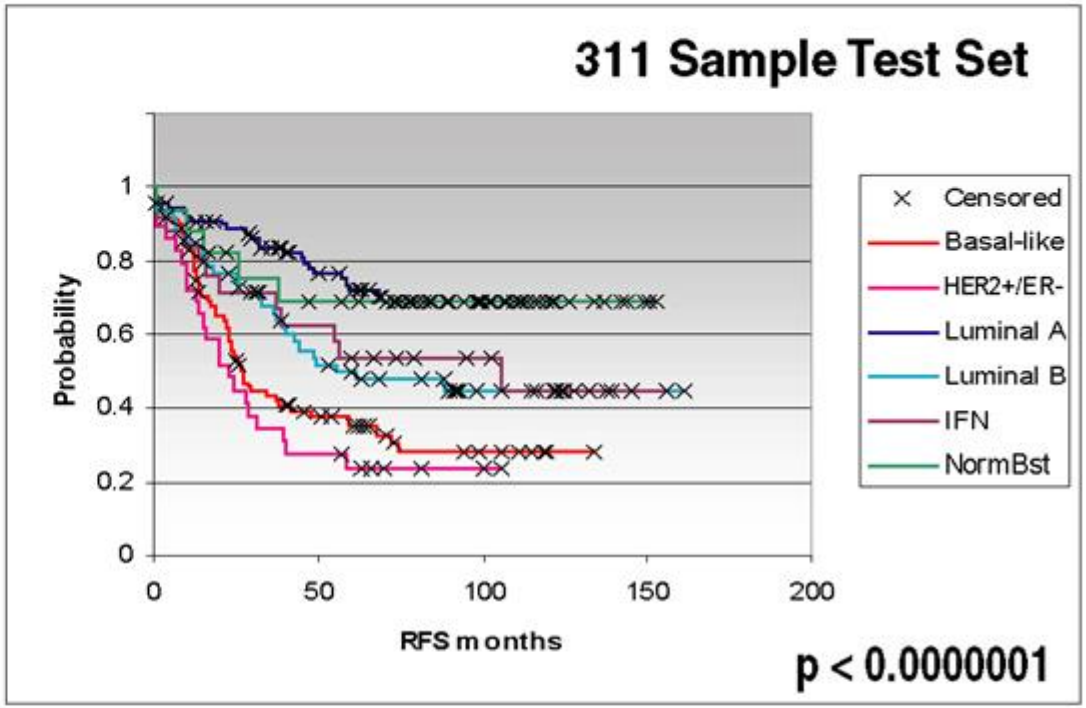
- 4 families of HER2+ breast cancer


HER2+/ER- Tumors
1. 15-25% of tumors
2. prognostic/predictive
3. two types (ER -/+)
4. Topo2 and/or cmyc amplif
HER2
Basal
Luminal
Proliferation
HER2
GRB7
17q11-12 amplification
AR





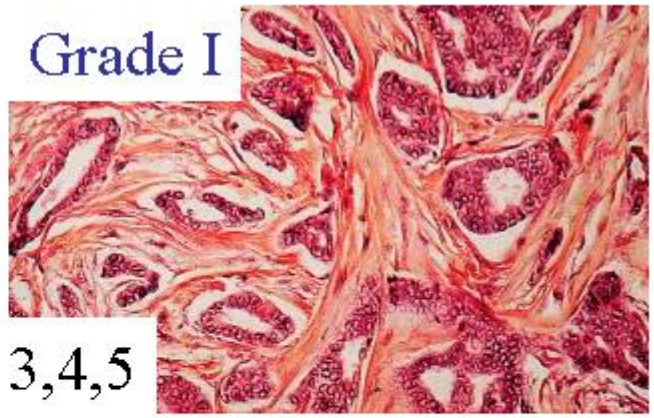
HER2+ is a poor prognosis factor

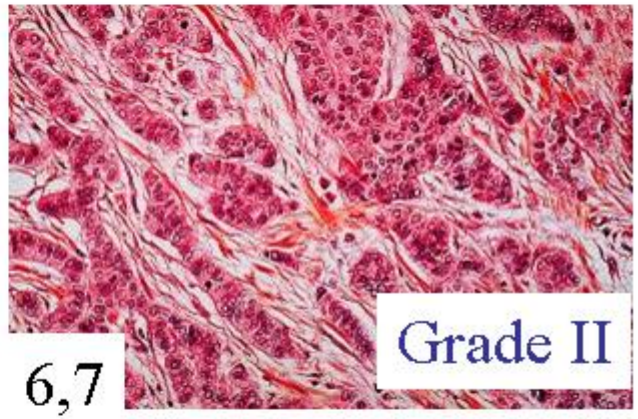
Genomic Grade
(Bottom-up approach)

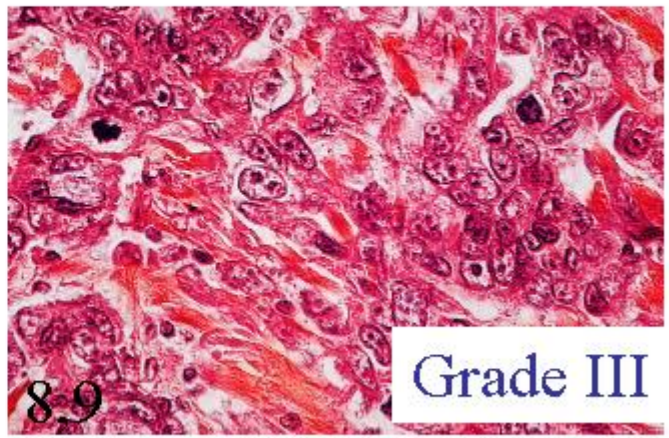
SBR grade modified by Elston and Ellis

60-70% are in the grade II / intermediate category

Use of mSBR to stratify grade II





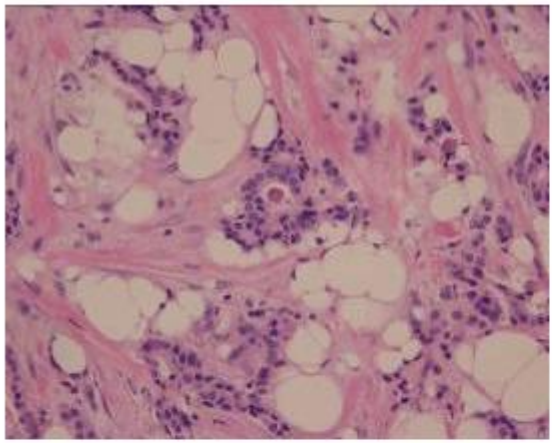


Institut Jules Bordet

Genomic Grade

(Bottom-up Approach)

Histological Grade

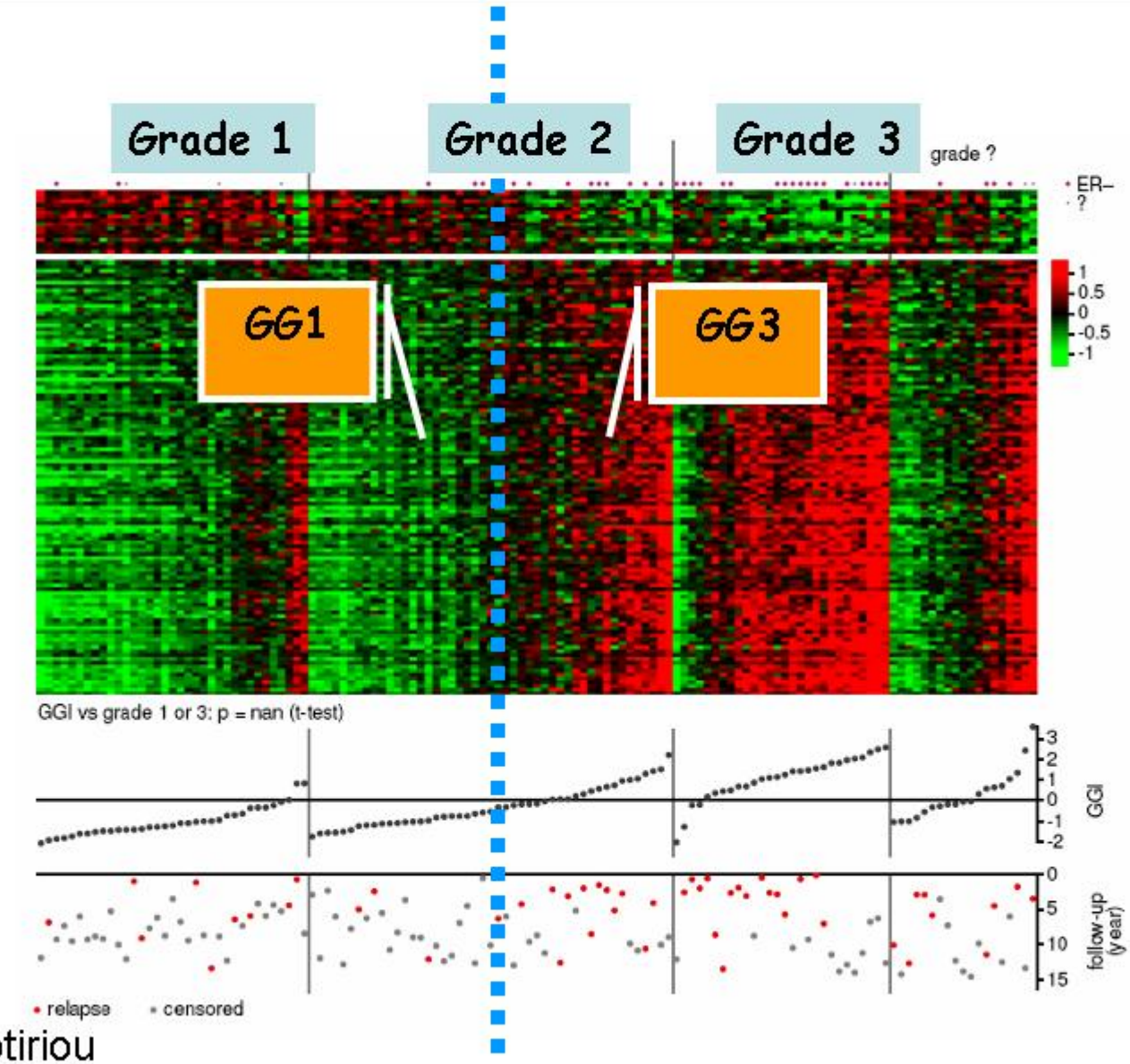


Grade 1 → "Low" Risk

Grade 2 → ?

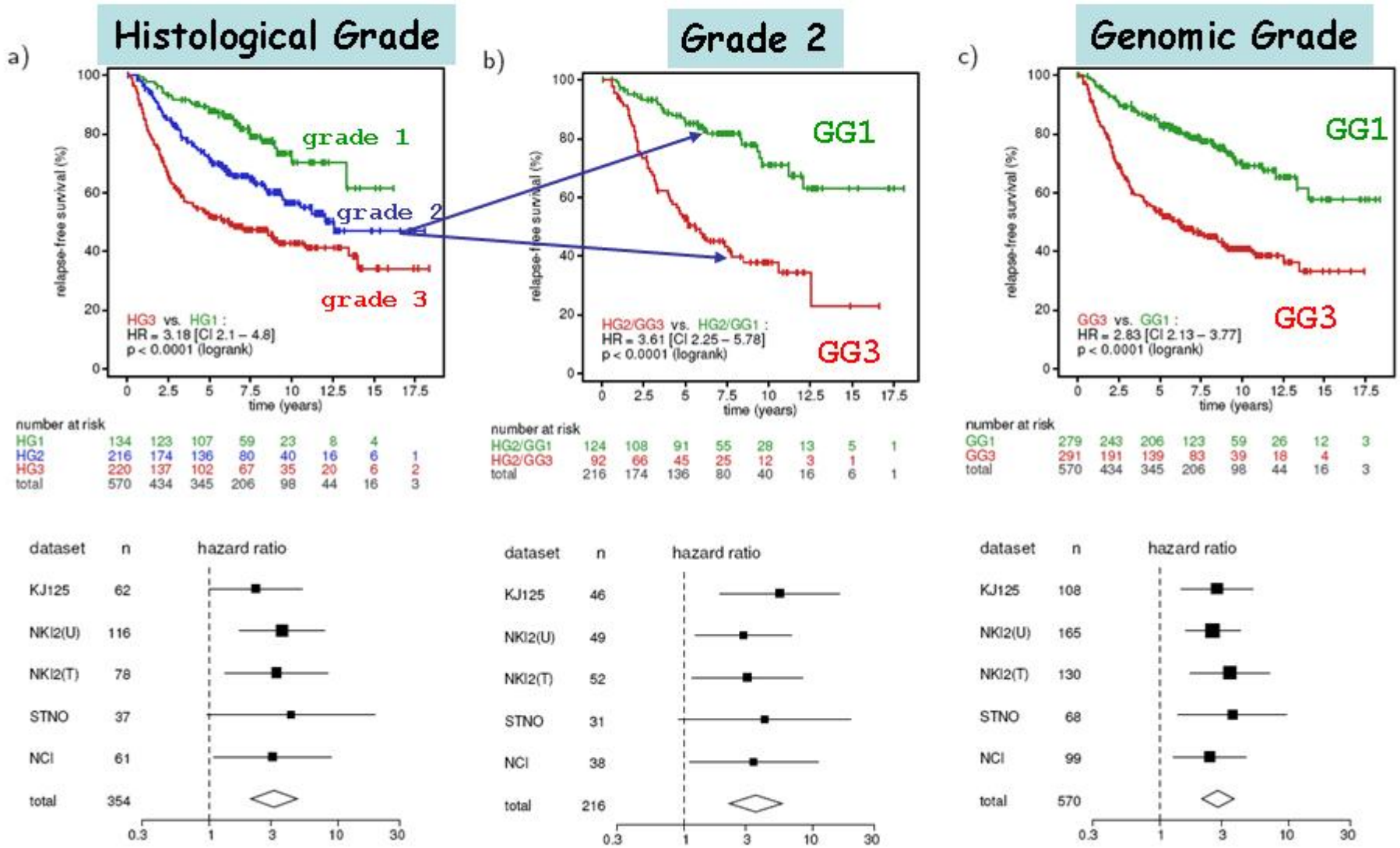
Grade 3 → "High" Risk

Genomic Grade (GG) in the Validation Set
N=125



Courtesy C Sotiriou

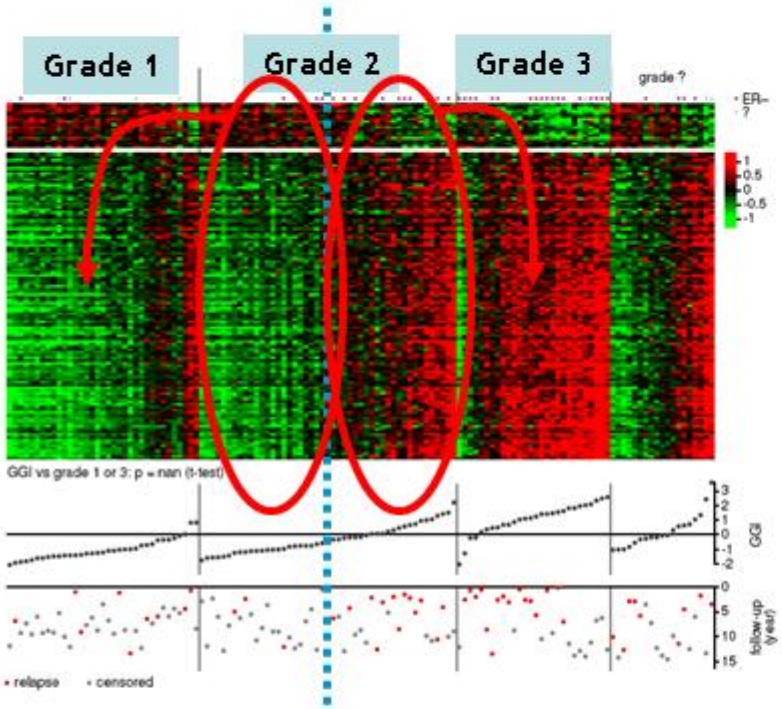
GG and Clinical Outcome



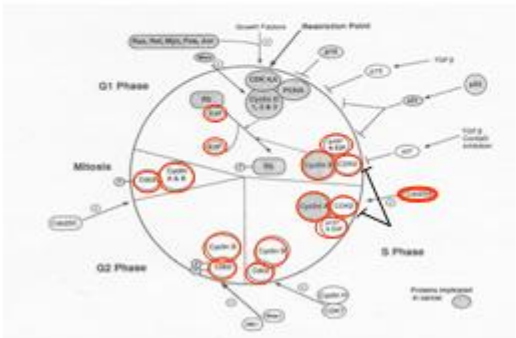
Courtesy C Sotiriou

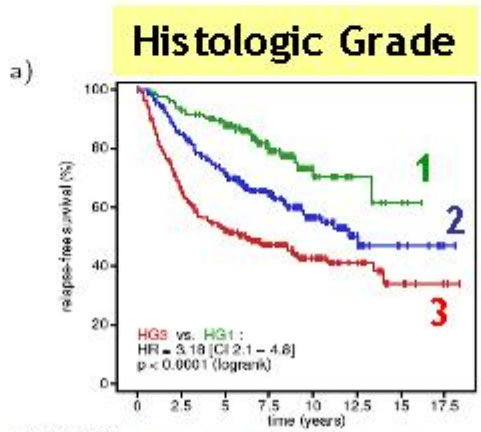
Genomic Grade

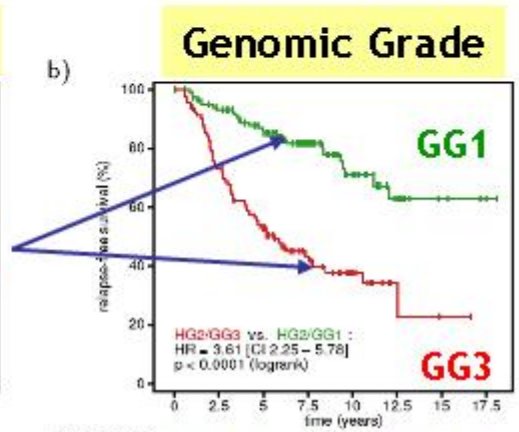
(Bottom-up Approach)

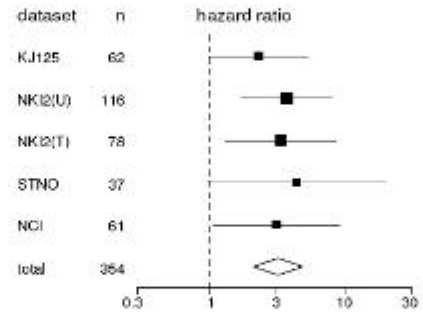


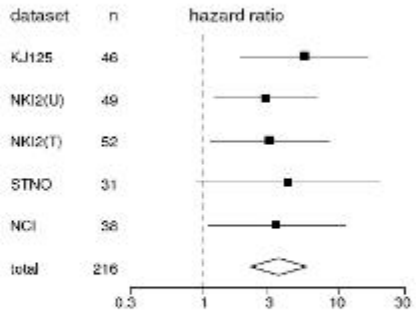
Genomic Grade=Proliferation genes











Sotiriou et al. J Natl Cancer Inst. 2006 Feb 15;98(4):262-72

TRANSBIG Validation Series

Multivariate Cox Analysis (DMFS) N=198 pts

	GENE70		GENE76		GGI	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≤ or >50years)	**1.4 (0.74-2.6)**	**0.3**	**1.7 (0.95-3.2)**	**0.075**	**1.6 (0.89-3)**	**0.11**
Tumor Size (≤ or >2cm)	**1.3 (0.67-2.4)**	**0.46**	**1.2 (0.66-2.4)**	**0.5**	**1.1 (0.59-2.1)**	**0.73**
ER status	**0.85 (0.43-1.6)**	**0.63**	**0.6 (0.31-1.2)**	**0.17**	**0.83 (0.43-1.6)**	**0.58**
Grade	**0.89 (0.28-2.8)**	**0.85**	**1.51 (0.46-4.8)**	**0.5**	**0.65 (0.2-2.1)**	**0.48**
Risk according to the gene signature	**7.2 (2.4-22)**	**$4x10^{-4}$**	**3.2 (1.3-7.7)**	**$9x10^{-3}$**	**6.3 (2.3-17)**	**$3x10^{-4}$**

Haibe-Kains et al. BMC Genomics, 2008

Clinical relevance of ER-positive luminal subtypes as defined by genomic grade

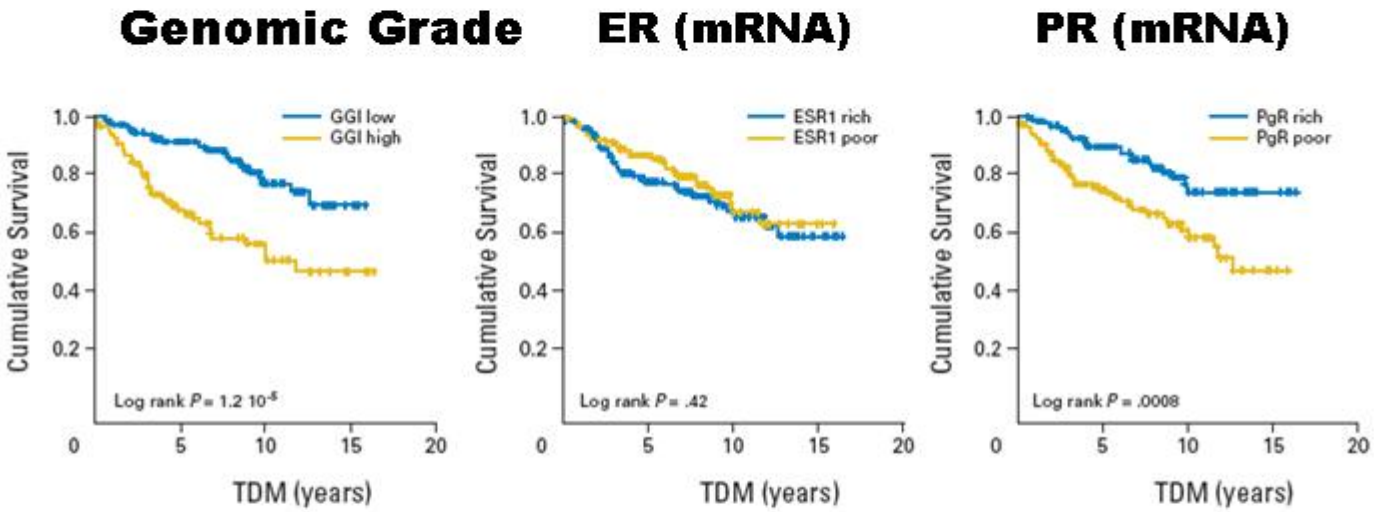


Table 2. Univariate and Multivariate Analysis of Breast Cancer Prognostic Markers (n = 249) in Adjuvant Tamoxifen-Treated Patients

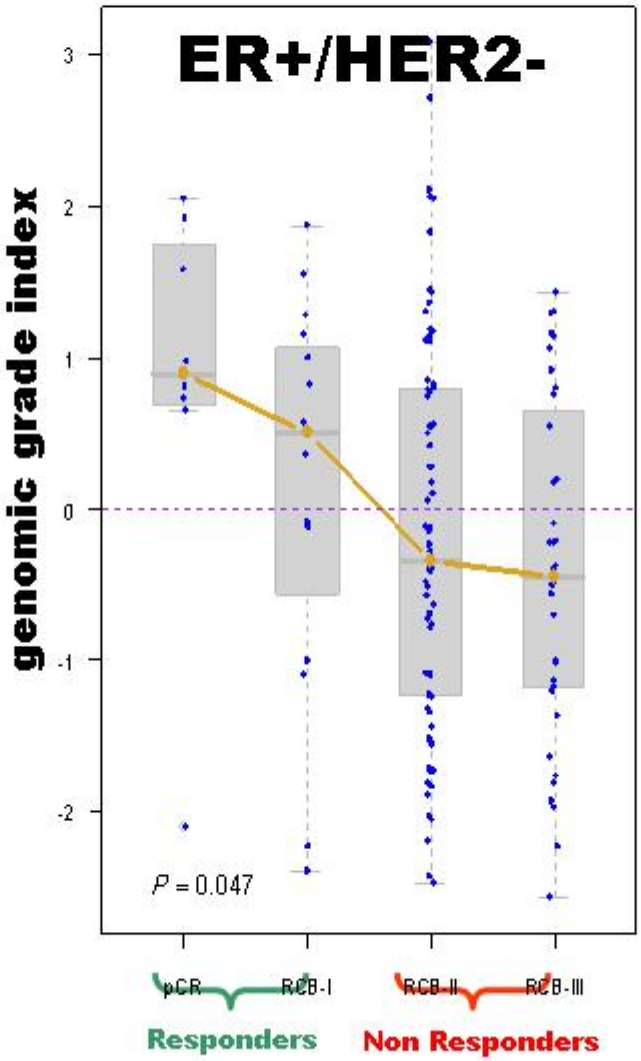
Variable	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P*	Hazard Ratio	95% CI	P*
Age: ≤ 50 *v* > 50 years	1.18	0.42 to 3.29	.75	1.06	0.30 to 3.73	.92
Size: > 2 *v* ≤ 2 cm	1.94	1.14 to 3.30	.01	1.56	0.84 to 2.92	.16
Histologic grade			.034			.30
1 *v* 2 + 3	3.32	1.32 to 8.38		1.88	0.69 to 5.09	
1 + 2 *v* 3	1.50	0.78 to 2.88		0.69	0.33 to 1.43	
Nodal status: positive *v* negative	1.44	0.84 to 2.49	.18	1.02	0.55 to 1.88	.96
Estrogen receptor: rich *v* poor	0.82	0.50 to 1.34	.42	0.95	0.54 to 1.69	.86
Progesterone receptor: rich *v* poor	0.42	0.25 to 0.70	.00096	0.68	0.38 to 1.24	.20
Genomic grade: high *v* low	3.24	1.93 to 5.43	.0000083	2.50	1.28 to 4.90	.0074

*Based on Cox regression and stratified according to the data sets.

Loi et al. JCO 2007

High genomic grade index is associated with higher response rate to preoperative chemotherapy

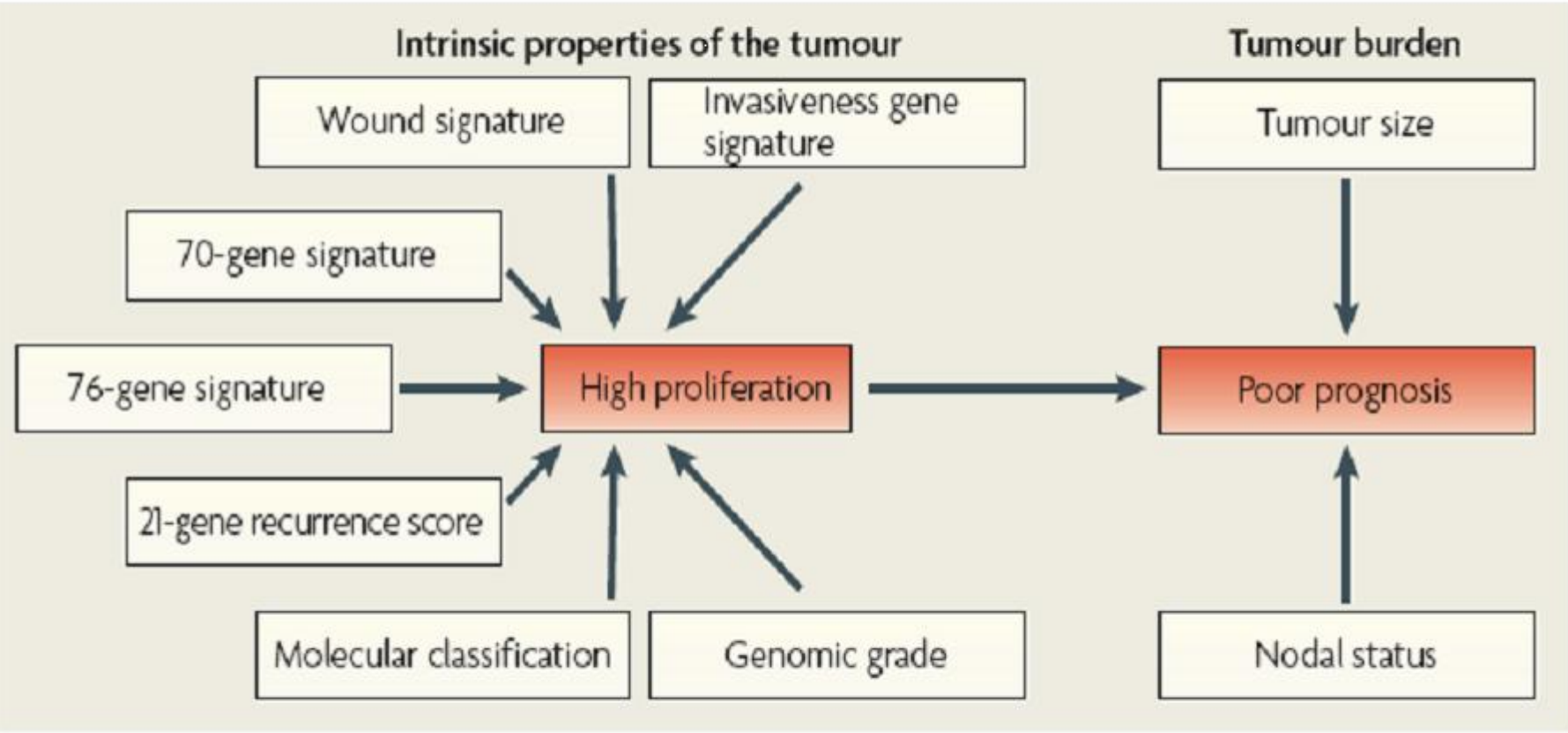
MDAnderson cohort (paclitaxel 12x → FAC 4x)



Grade

- Pros
  - Tumor grade is a major prognosis factor
  - Grade III are more prone to pCR when neoadjuvant treatment (predictive)
  - Proliferation is linked to tumor grade
- Cons
  - Grade is a poorly reproducible factor
  - Grade II tumors are heterogenous => molecular grade> histological grade
  - Proliferation is better evaluated by molecular assays

High proliferation is well estimated by mitotic count and/or Ki67, isn't it ?

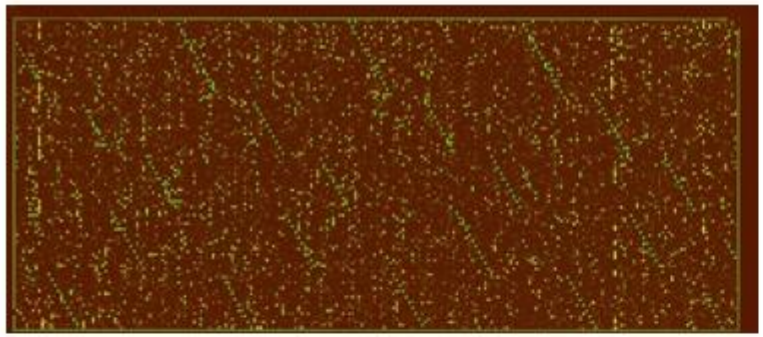
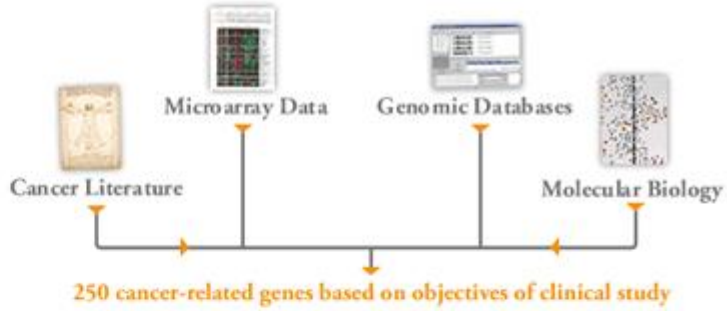


Sotiriou C, Piccart M. Nat Cancer Review 2007

Signatures used in clinical practise

mammaprint™

oncotype DX Breast Cancer Assay

Full genome analysis	250 candidate genes
	
70 genes:	**16 genes**
Good or poor prognosis	**RS : low, intermediate, high**

MammaPrint®, Agendia (Top-Down approach)

Gene expression profiling predicts clinical outcome of breast cancer

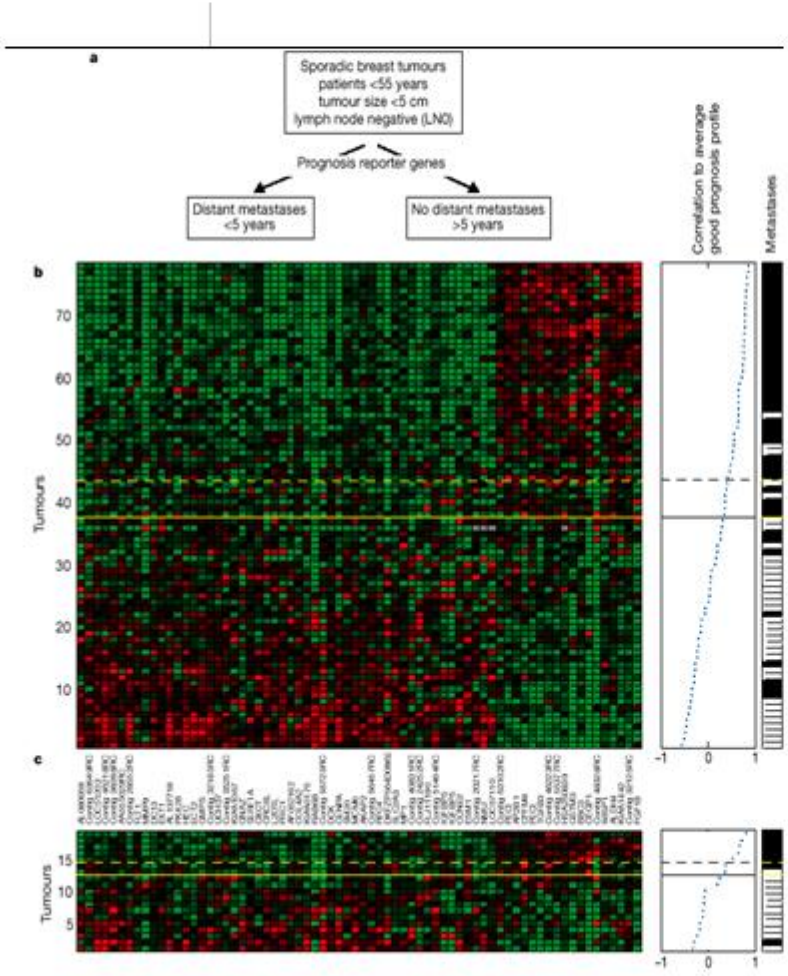
Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†, Yudong D. He‡, Augustinus A. M. Hart*, Mao Mao‡, Hans L. Peterse*, Karin van der Kooy*, Matthew J. Marton‡, Anke T. Witteveen*, George J. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

NATURE | VOL 415 | 31 JANUARY 2002 | www.nature.com

Supervised

Learning set: 78

Validation set: 19



→ 70 gènes

↓

2 groups of different prognosis

Avoid over treatment

Table 1 Breast cancer patients eligible for adjuvant systemic therapy

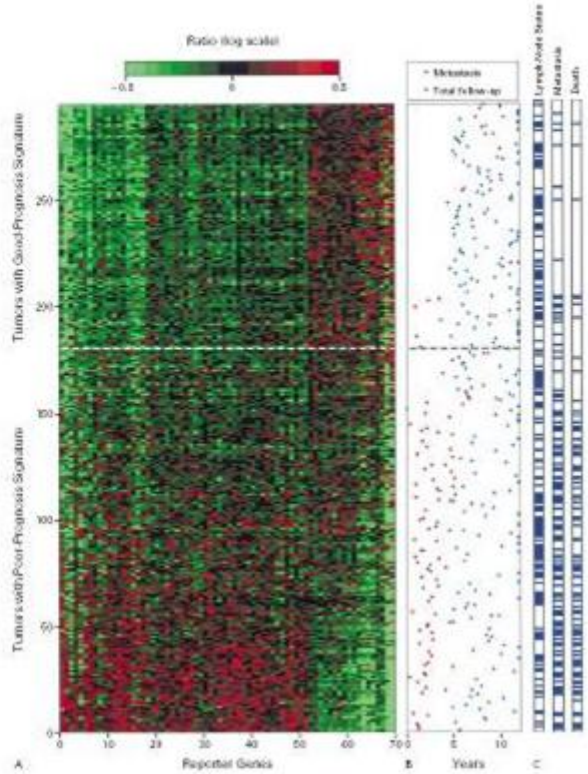
Consensus	Patient group: Total patient group (*n* = 78)	Metastatic disease at 5 yr (*n* = 34)	Disease free at 5 yr (*n* = 44)
St Gallen	64/78 (82%)	33/34 (97%)	31/44 (70%)
NIH	72/78 (92%)	32/34 (94%)	40/44 (91%)
Prognosis profile*	43/78 (55%)	31/34 (91%)	12/44 (27%) (18/44 (41%)†)

The New England
Journal of Medicine

VOLUME 347 DECEMBER 19, 2002 NUMBER 25

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

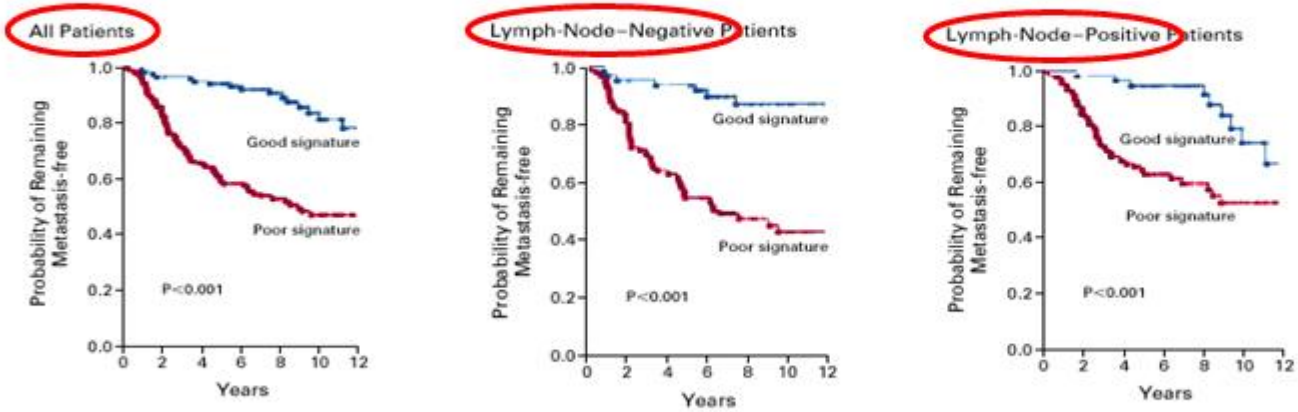
MARC J. VAN DE VIJVER et al



25.000 genes / Agilent Platform - 295 **localized T**

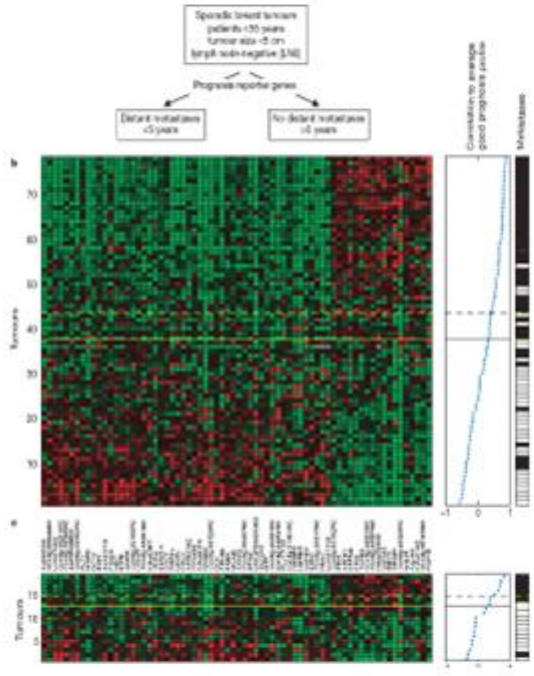
pT1-2, age < 52 years, good and bad prognosis

Validation of the 70 gene predictor



Median follow up 6,7 ans

70-gene good prognostic signature (Top-down approach)



Van't Veer et al. Nature, 2002

1st Validation Study

van de Vijver MJ, et al. N Engl J Med, 2002

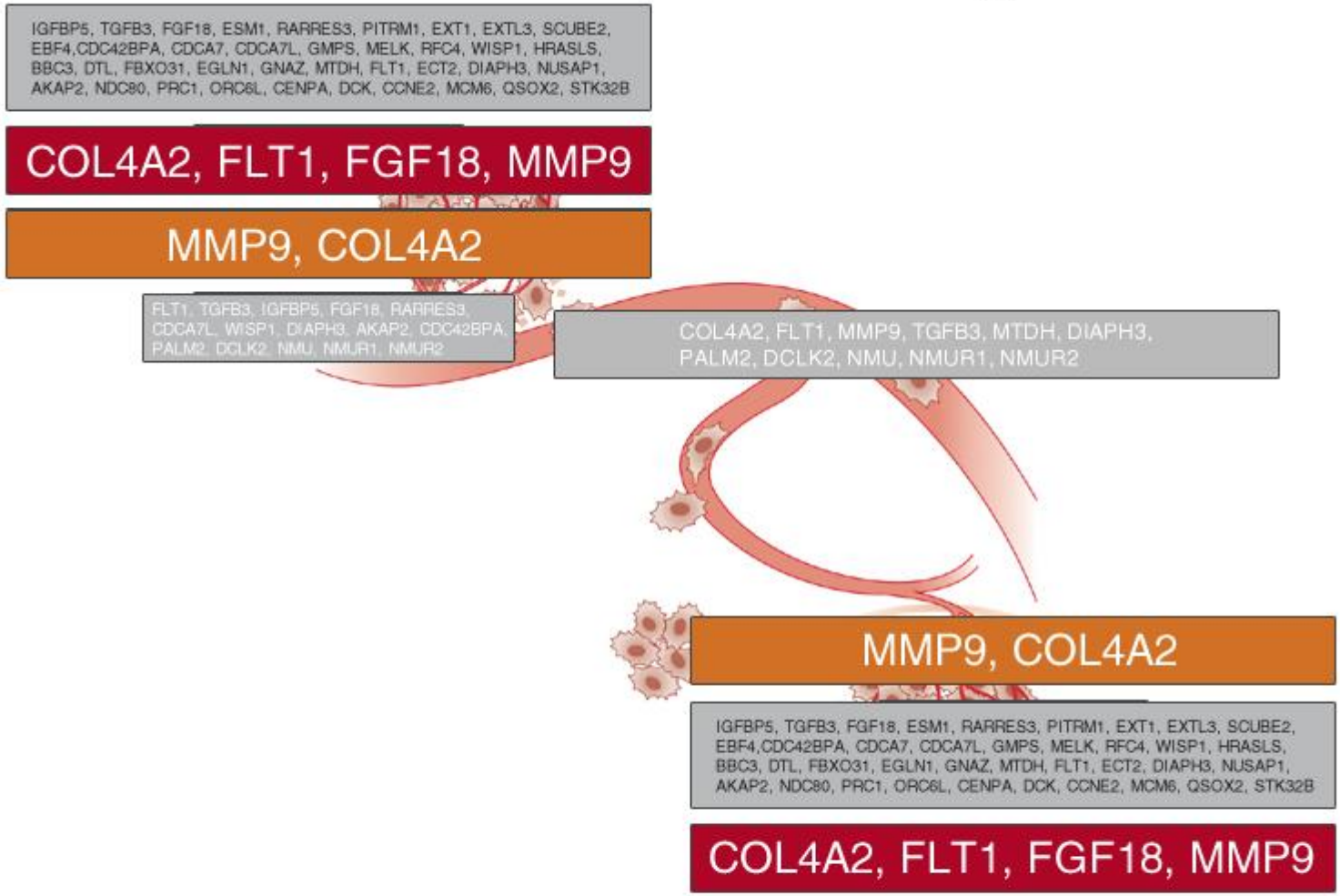
TABLE 3. RATE OF OVERALL SURVIVAL AND THE PROBABILITY THAT PATIENTS WOULD REMAIN FREE OF DISTANT METASTASES AT 5 AND 10 YEARS, ACCORDING TO THE PROGNOSIS SIGNATURE.*

GROUP	NO. OF PATIENTS	FREE OF DISTANT METASTASES		OVERALL SURVIVAL	
		5 YR	10 YR	5 YR	10 YR
		percent			
All patients					
Good-prognosis signature	115	94.7±2.1	85.2±4.3	97.4±1.5	94.5±2.6
Poor-prognosis signature	180	60.5±3.8	50.6±4.5	74.1±3.3	54.6±4.4
Patients with lymph-node–negative disease					
Good-prognosis signature	60	93.4±3.2	86.8±4.8	96.7±2.3	96.7±2.3
Poor-prognosis signature	91	56.2±5.5	44.1±6.3	71.5±4.8	49.6±6.1
Patients with lymph-node–positive disease					
Good-prognosis signature	55	95.2±2.6	82.7±7.8	98.2±1.8	92.0±4.8
Poor-prognosis signature	89	66.3±5.2	56.7±6.4	76.5±4.6	59.5±6.3

*Distant metastasis was a first event. Plus–minus values are means ±SE.

MammaPrint®, Agendia

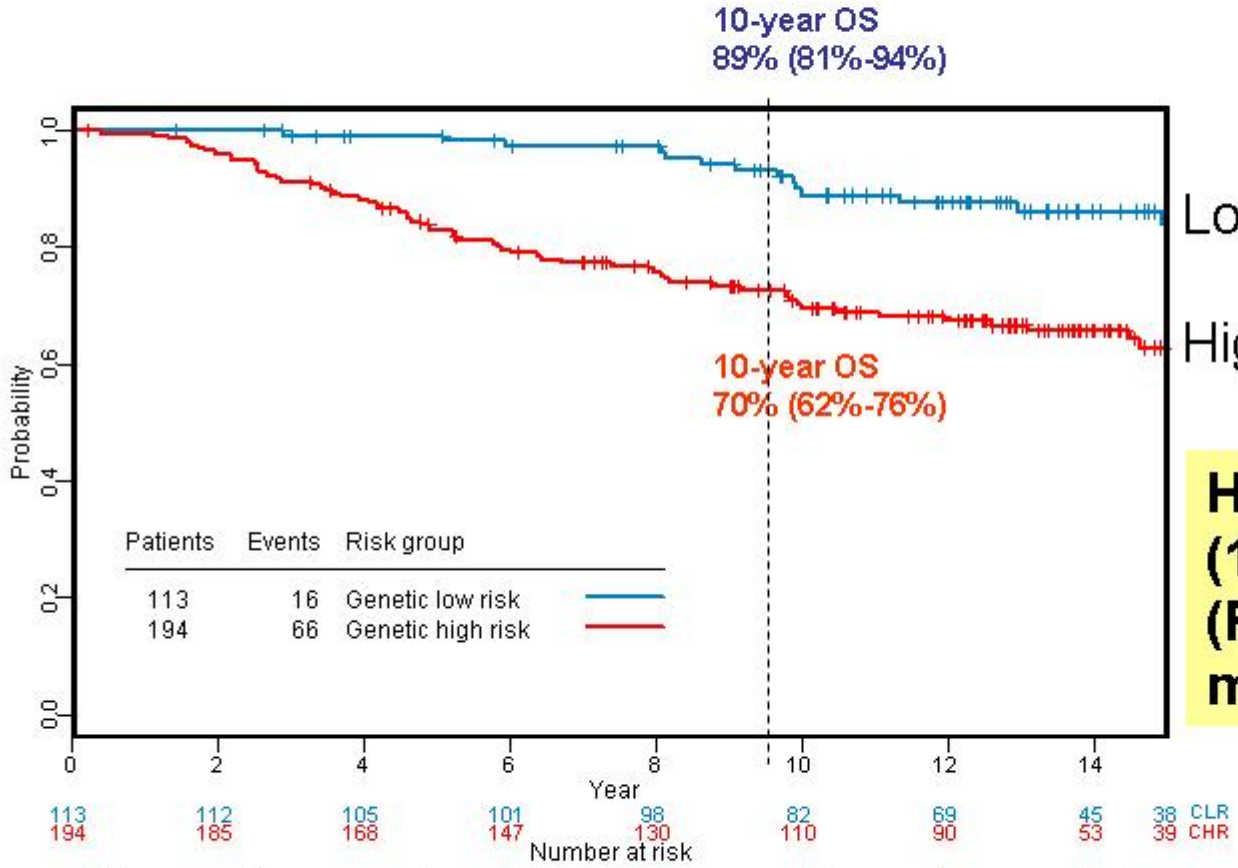
Known functions of the 70 genes



Cover all of the metastatic processes

International validation of MammaPrint

5 European Hospitals, retrospective series, 302 untreated pts



Low risk profile

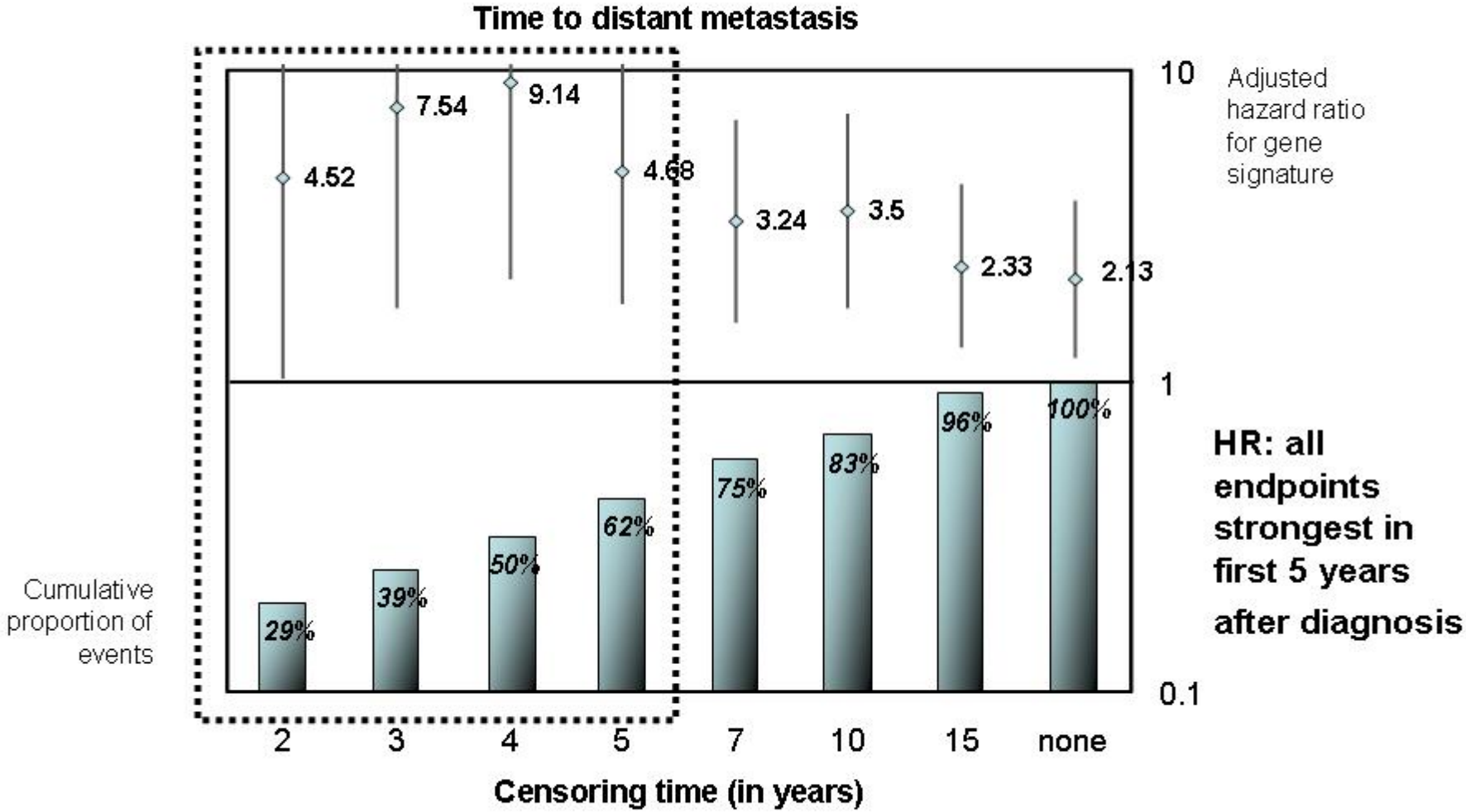
High risk profile

HR 2.87 (1.66-4.96) (P<0.001) multivariate

Overall survival by gene signature risk

JNCI 98, p1183-1192, 2006

MammaPrint predicts outcome of breast cancer during first 5 years

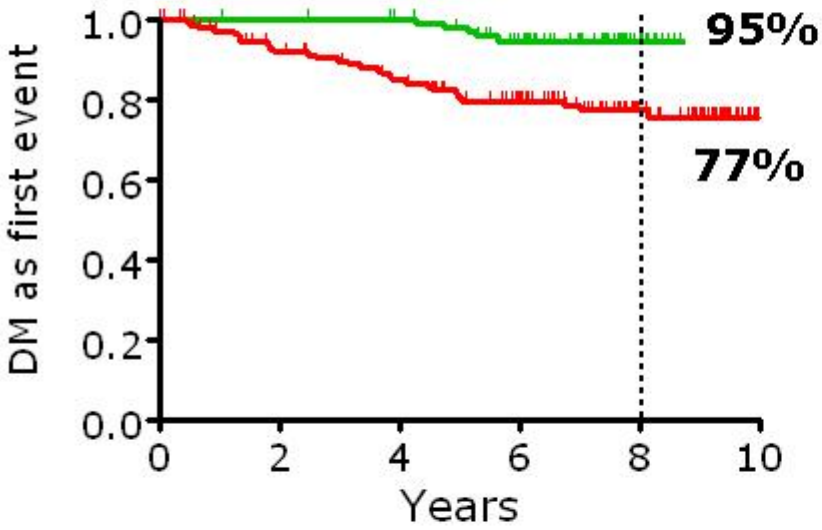


Buyse et al., *Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer*, Journal of the National Cancer Institute, Vol 98, No. 17, 2006

MammaPrint in patients with 1-3 positive lymph nodes

Good profile (n=99) (41%)
Poor profile (n=142) (59%)

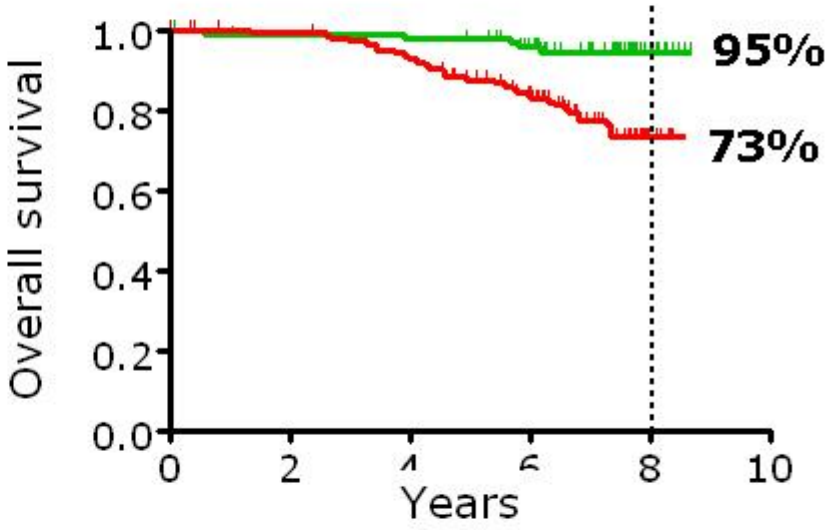
Distant metastases as first event



HR 4.1

(95%CI 1.7 – 10.0), p=0.002

Overall survival



HR 5.4

(95%CI 2.1 – 13.8), p<0.001

Adjuvant treatment: 53% chemo, 64% hormonal

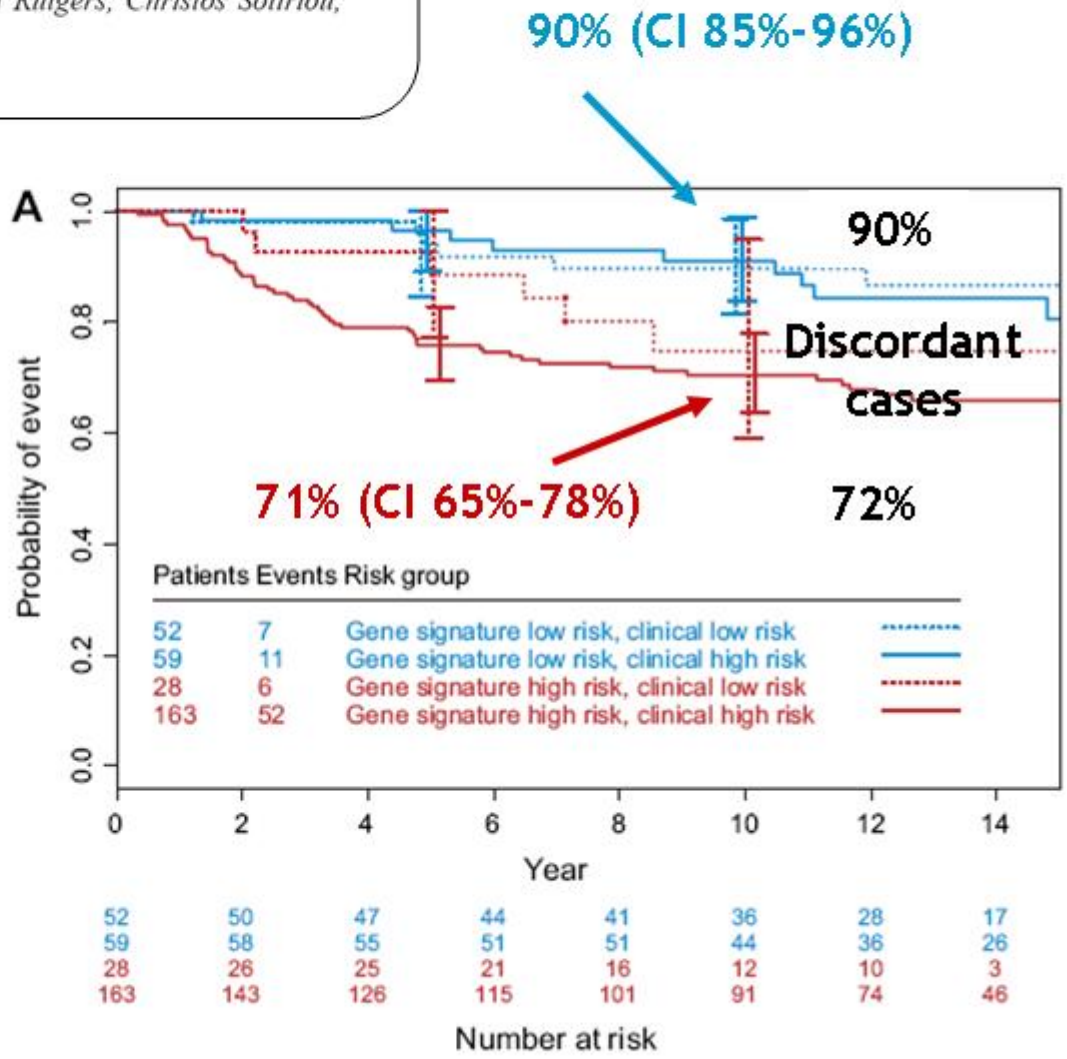
Mook et al, Breast Cancer Res Treat 2008

Validation and Clinical Utility of a 70-Gene Prognostic Signature for Women With Node-Negative Breast Cancer

Marc Buyse, Sherene Loi, Laura van't Veer, Giuseppe Viale, Mauro Delorenzi, Annuska M. Glas, Mahasti Saghatchian d'Assignies, Jonas Bergh, Rosette Lidereau, Paul Ellis, Adrian Harris, Jan Bogaerts, Patrick Therasse, Arno Floore, Mohamed Amakrane, Fanny Piette, Emiel Rutgers, Christos Sotiriou, Fatima Cardoso, Martine J. Piccart

On behalf of the TRANSBIG Consortium

30% of Discordant cases between Adjuvant!Online and signature



Buyse et al. J Natl Cancer Inst, 2006

Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER)

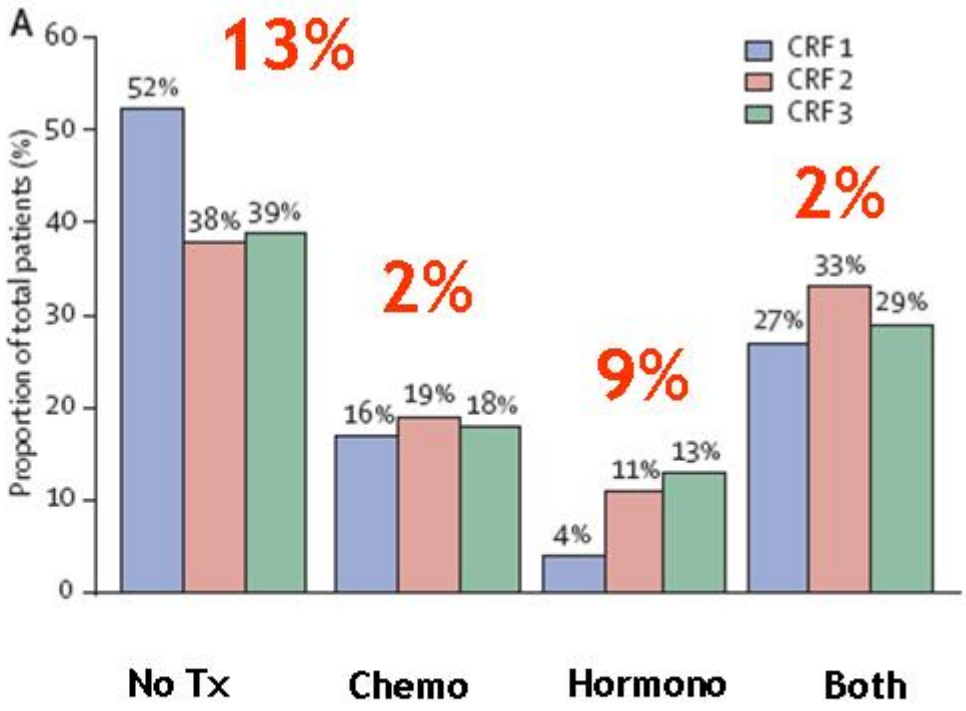
Jolien M Bueno-de-Mesquita, Wim H van Harten, Valesca P Retel, Laura J van 't Veer, Frits S A M van Dam, Kim Karsenberg, Kirsten F L Douma, Harm van Tinteren, Johannes L Peterse†, Jelle Wesseling, Tin S Wu, Douwe Atsma, Emiel J T Rutgers, Guido Brink, Arno N Floore, Annuska M Glas, Rudi M H Roumen, Frank E Bellot, Cees van Krimpen, Sjoerd Rodenhuis, Marc J van de Vijver, Sabine C Linn

Treatment changed in 24% of the patients!

30% - 39% of discordant cases

High Risk patients

St Gallen: 87%
Dutch guidelines: 43%
70-gene signature: 49%



Bueno-de-Mesquita et al. Lancet Oncology, 2007

Oncotype DX™

Oncotype DX™ 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

INVASION
Stromelysin 3
Cathepsin L2

GSTM1

BAG1

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

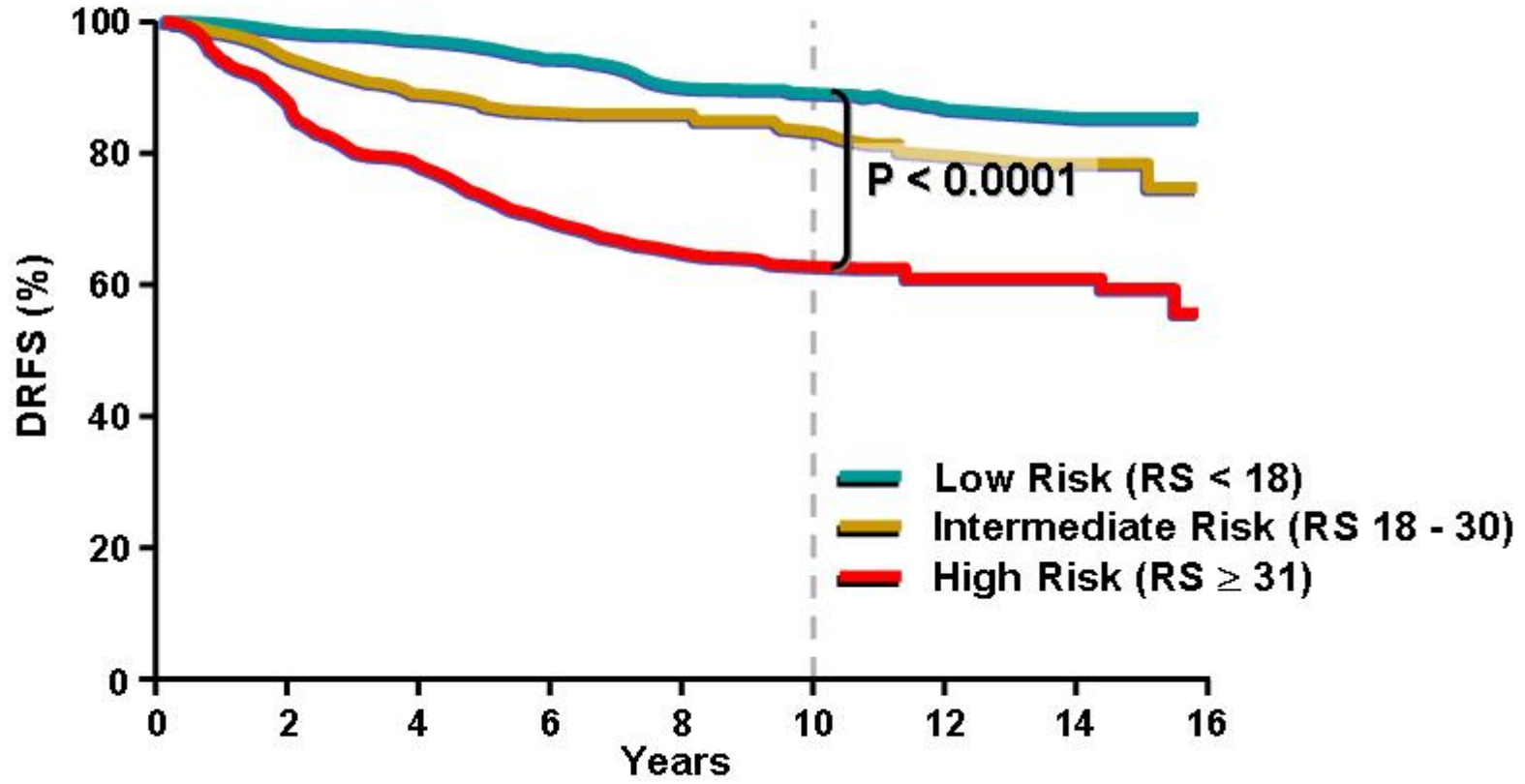
RS =
+ 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0-100)
Low risk	RS <18
Int risk	RS ≥18 and <31
High risk	RS ≥31

Oncotype DX

Multi-gene RT-PCR Assay for Predicting Recurrence in Node Negative Breast Cancer Patients - NSABP B-14 Study.

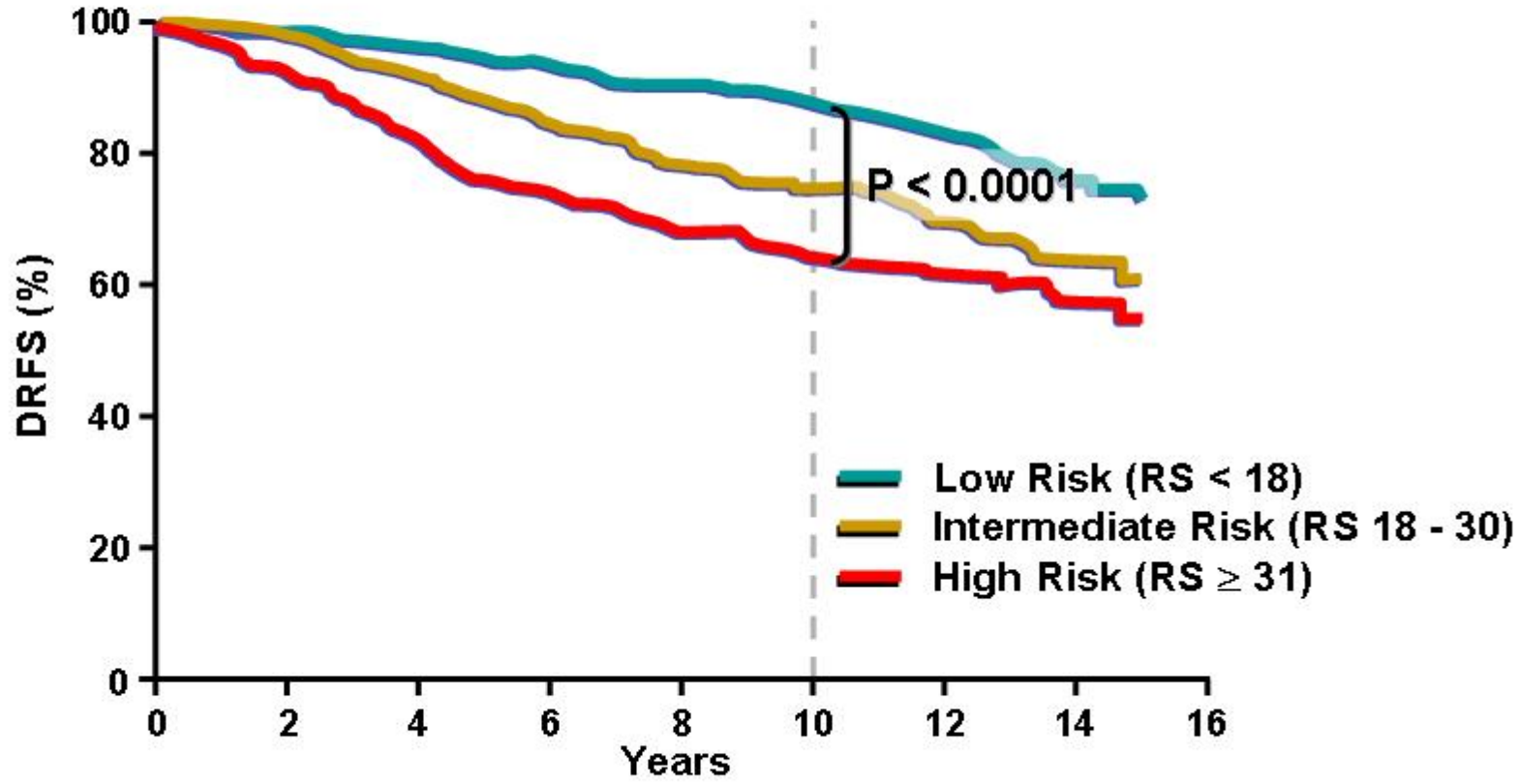
Results: **Relapse-Free Survival (%)**



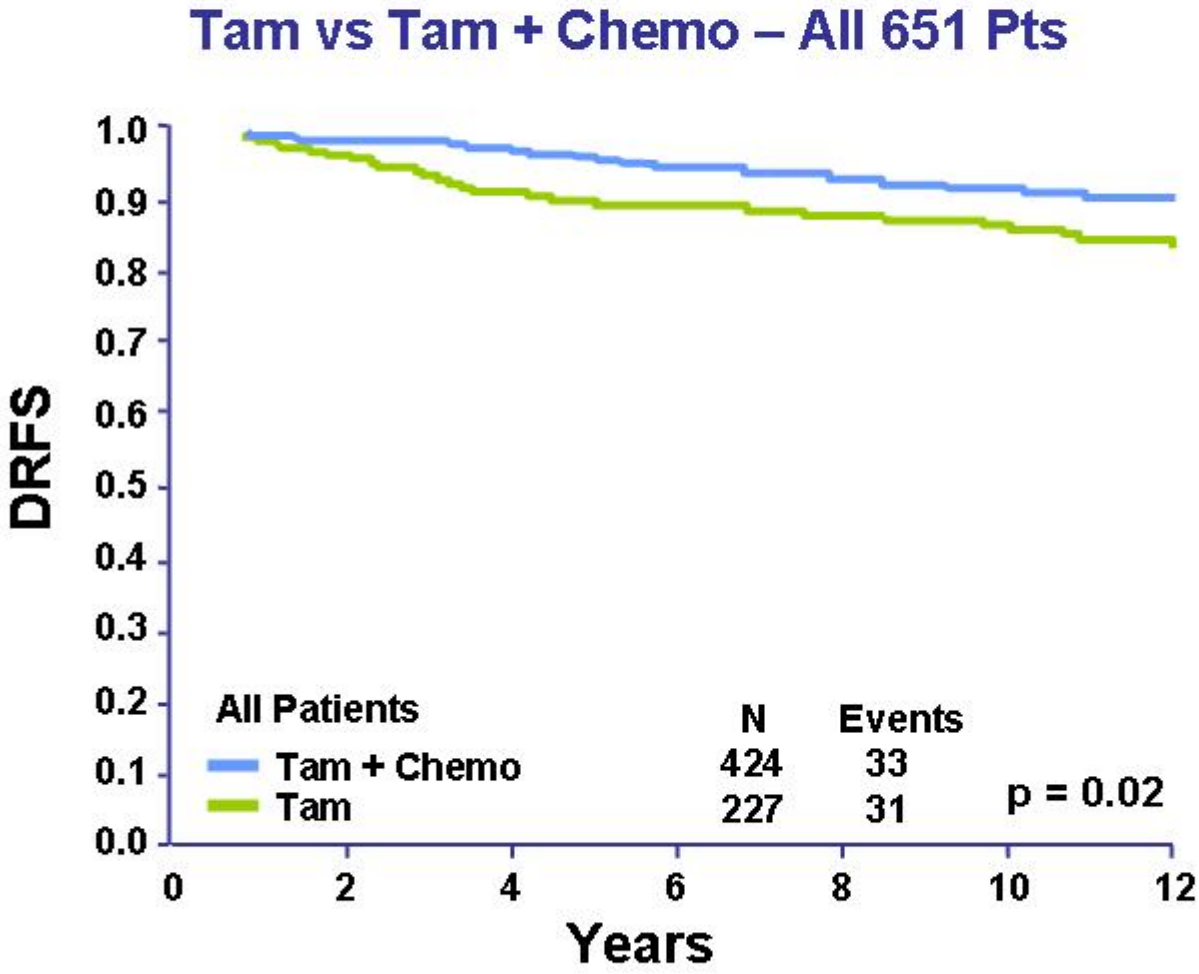
Oncotype DX

Multi-gene RT-PCR Assay for Predicting Recurrence in Node Negative Breast Cancer Patients - NSABP B-14 Study.

Results: **Over-All Survival (%)**

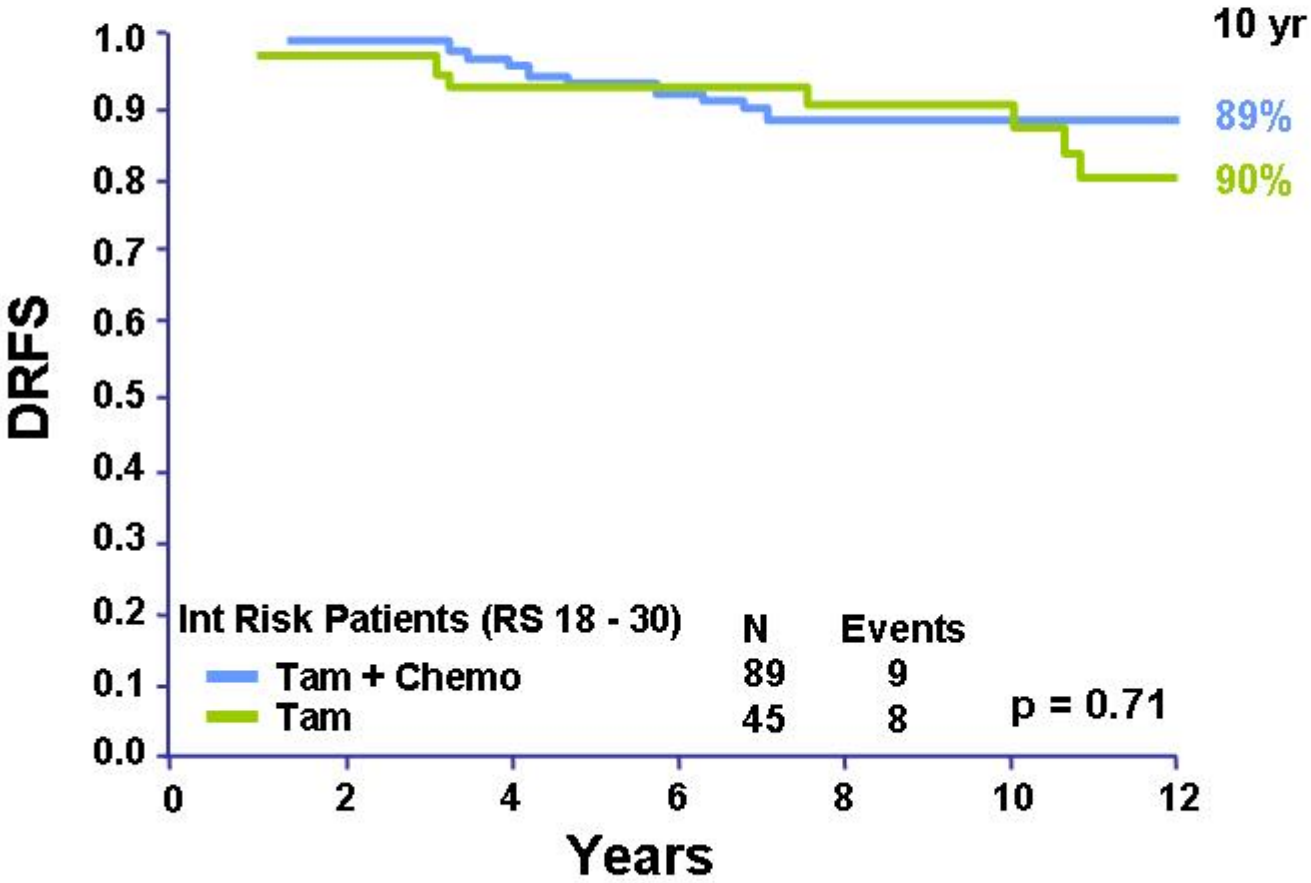


B-20 Results


Tam vs Tam + Chemo – All 651 Pts
DRFS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Patients
N
Events
Tam + Chemo
424
33
Tam
227
31
p = 0.02
0
2
4
6
8
10
12
Years

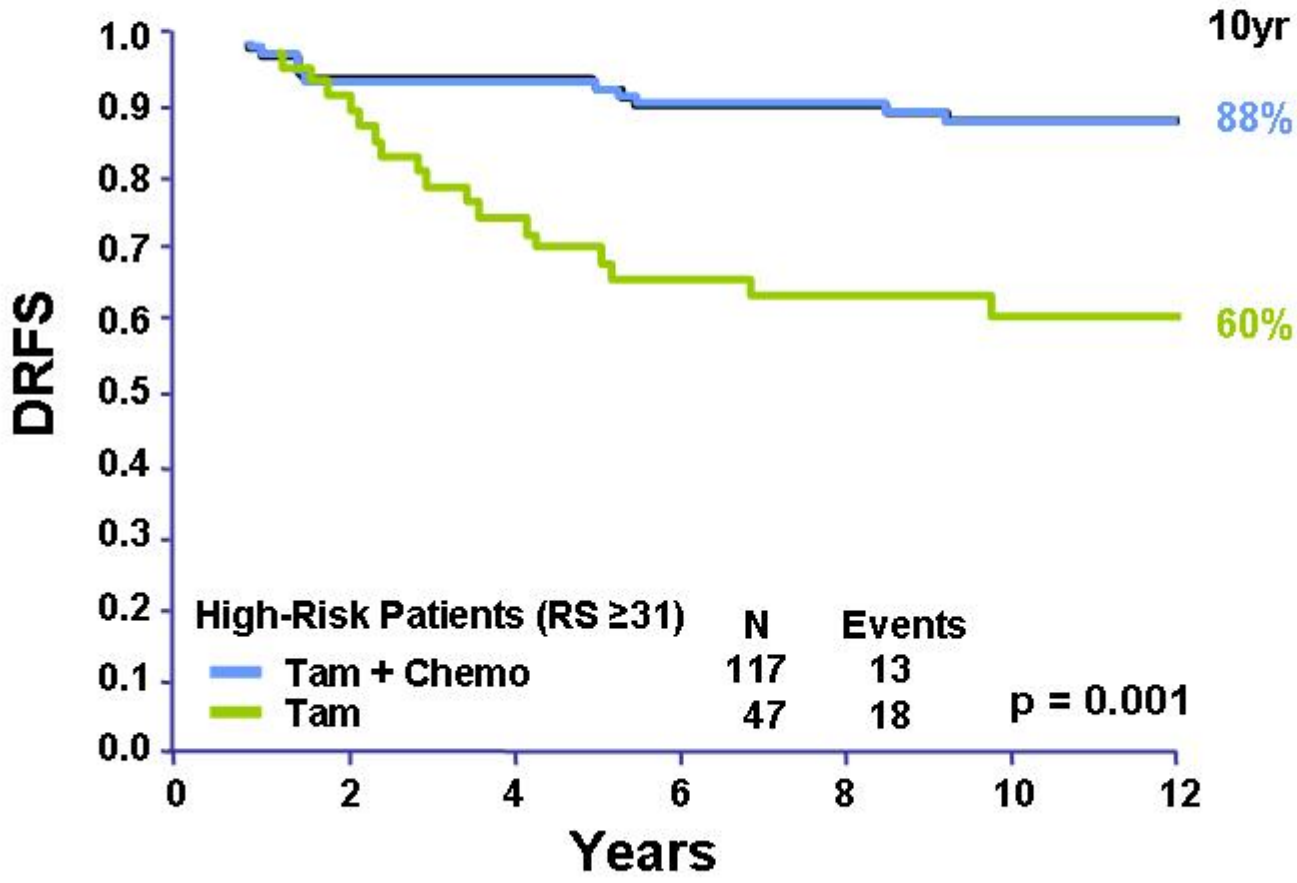
B-20 Results

Tam vs Tam + Chemo – Intermediate Risk (RS 18-30)



B-20 Results

Tam vs Tam + Chemo – High Risk (RS ≥31)

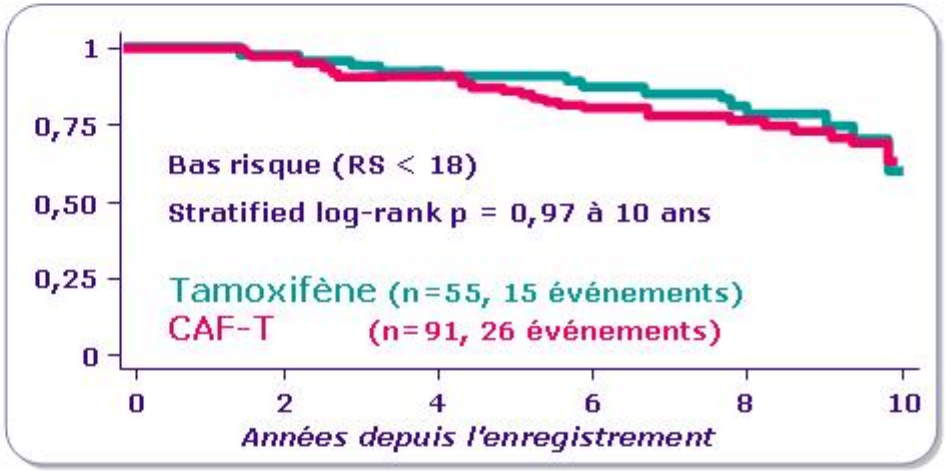


Oncotype DX predictive value 10yrs SSM

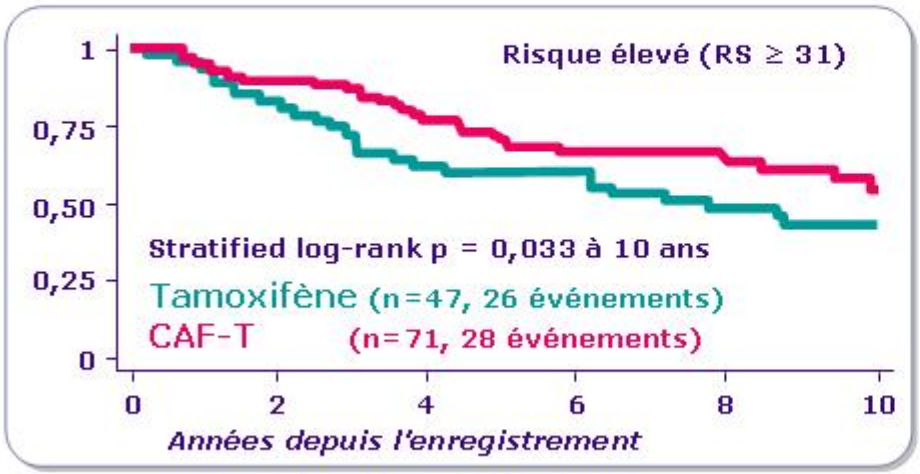
INT0100 study

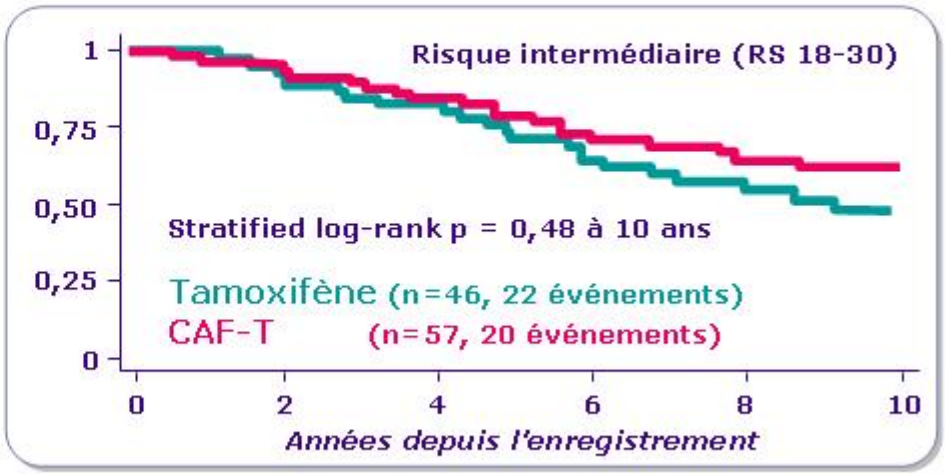
SSM

No benefit if low risk



Important benefit if high risk

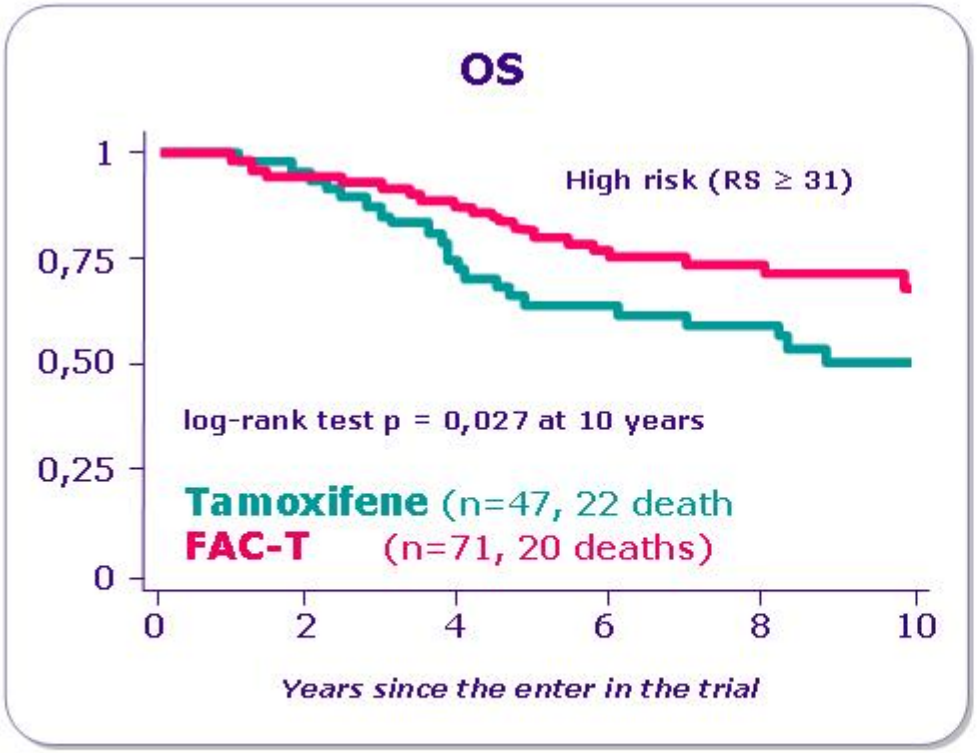




Albain K. et al. SABCS 2007, Abstract 10 http://www.abstracts2view.com/sabcs/view.php?nu=SABCS07L_1165&terms=

Oncotype DX prognostic value for 10yrs OS INT0100 study

- **no benefit of FAC if low RS**
  - **In the first 5 yrs (HR 1,05)**
  - **and during all the observation period (HR 1,18)**



- **strong impact of FAC if high RS during the first 5yrs HR 0,43 (0,21; 0,90) and during all the observation period HR 0,56 (0,31; 1,01)**

10 yrs OS projections :

- ➔ **Tam 51% (35 %, 65 %)**
- ➔ **FAC-T 68% (51 %, 79 %)**

Albain K. et al. SABCS 2007, Abstract 10 http://www.abstracts2view.com/sabcs/view.php?nu=SABCS07L_1165&terms=

HOXB13/IL17BR
(Top-Down approach)

A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen

Xiao-Jun Ma,[1] Zuncai Wang,[2] Paula D. Ryan,[3] Steven J. Isakoff,[4,5] Anne Barmettler,[3] Andrew Fuller,[2] Beth Muir,[2] Gayatry Mohapatra,[2] Ranelle Salunga,[1] J. Todd Tuggle,[1] Yen Tran,[1] Diem Tran,[1] Ana Tassin,[1] Paul Amon,[1] Wilson Wang,[1] Wei Wang,[1] Edward Enright,[1] Kimberly Stecker,[1] Eden Estepa-Sabal,[1] Barbara Smith,[3] Jerry Younger,[3] Ulysses Balis,[3] James Michaelson,[3] Atul Bhan,[2] Karleen Habin,[3] Thomas M. Baer,[1] Joan Brugge,[4] Daniel A. Haber,[1] Mark G. Erlander,[1] and Dennis C. Sgroi[2]

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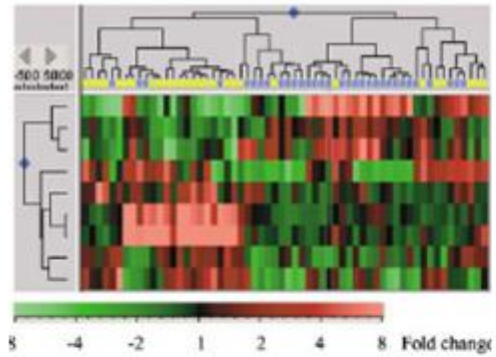
VOLUME 24 · NUMBER 28 · OCTOBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

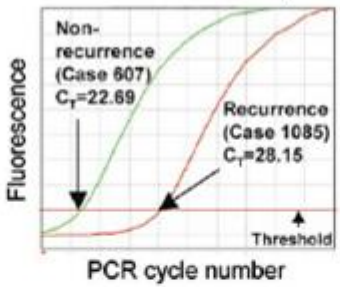
The *HOXB13:IL17BR* Expression Index Is a Prognostic Factor in Early-Stage Breast Cancer

Xiao-Jun Ma, Susan G. Hilsenbeck, Wilson Wang, Li Ding, Dennis C. Sgroi, Richard A. Bender, C. Kent Osborne, D. Craig Allred, and Mark G. Erlander

HOXB13/ IL17BR



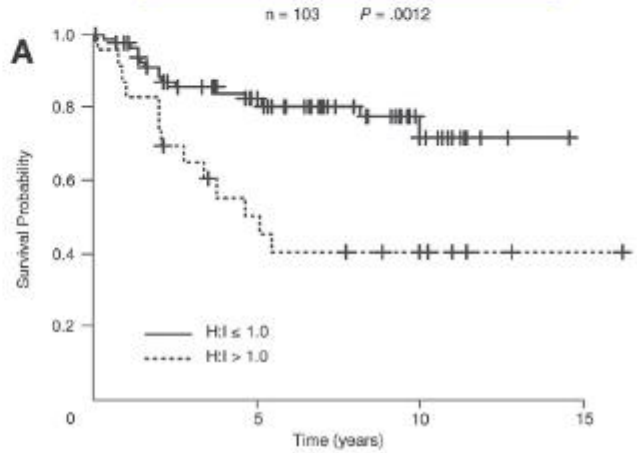
RT-PCR assay



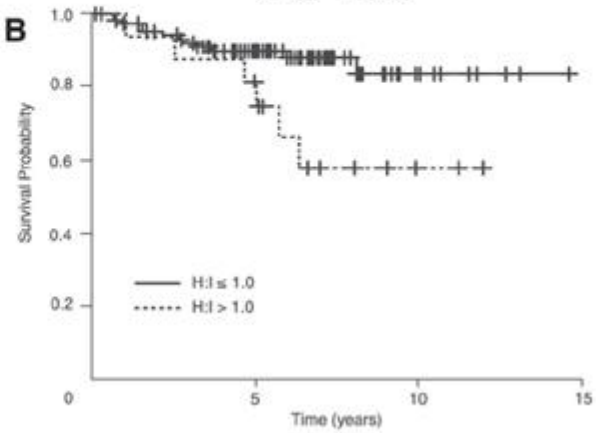
60 patients
primary breast cancer

Adjuvant Tamoxifen-treated
Minimal 5-year FU

Untreated

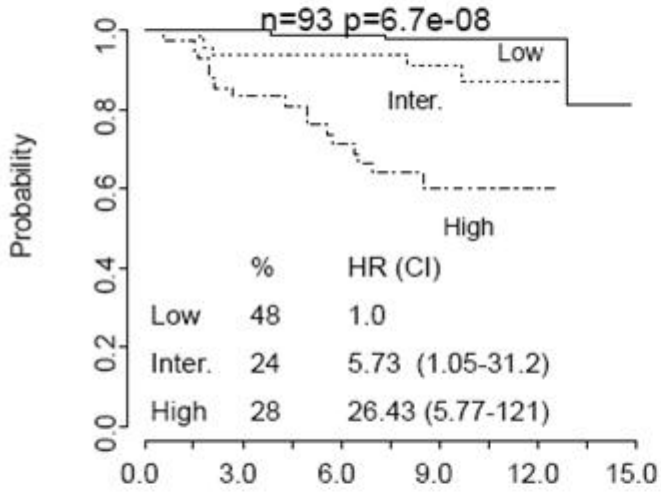


Tamoxifen-treated

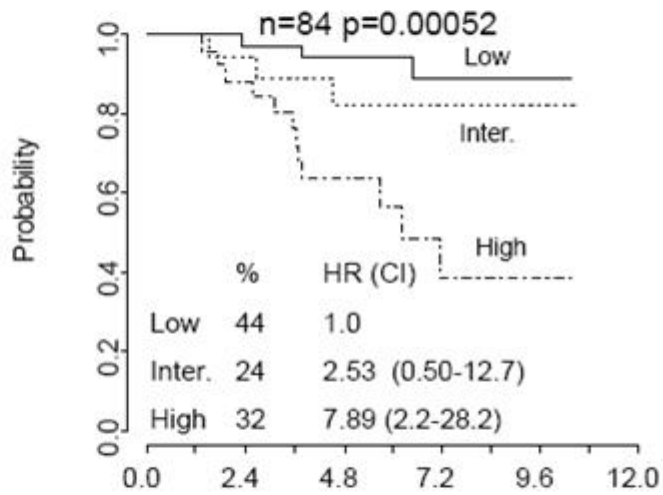


Molecular Grade Index + HOXB13/IL17BR= More accurate prognostic information

MGH dataset



JBI dataset



Low Risk : Low MGI

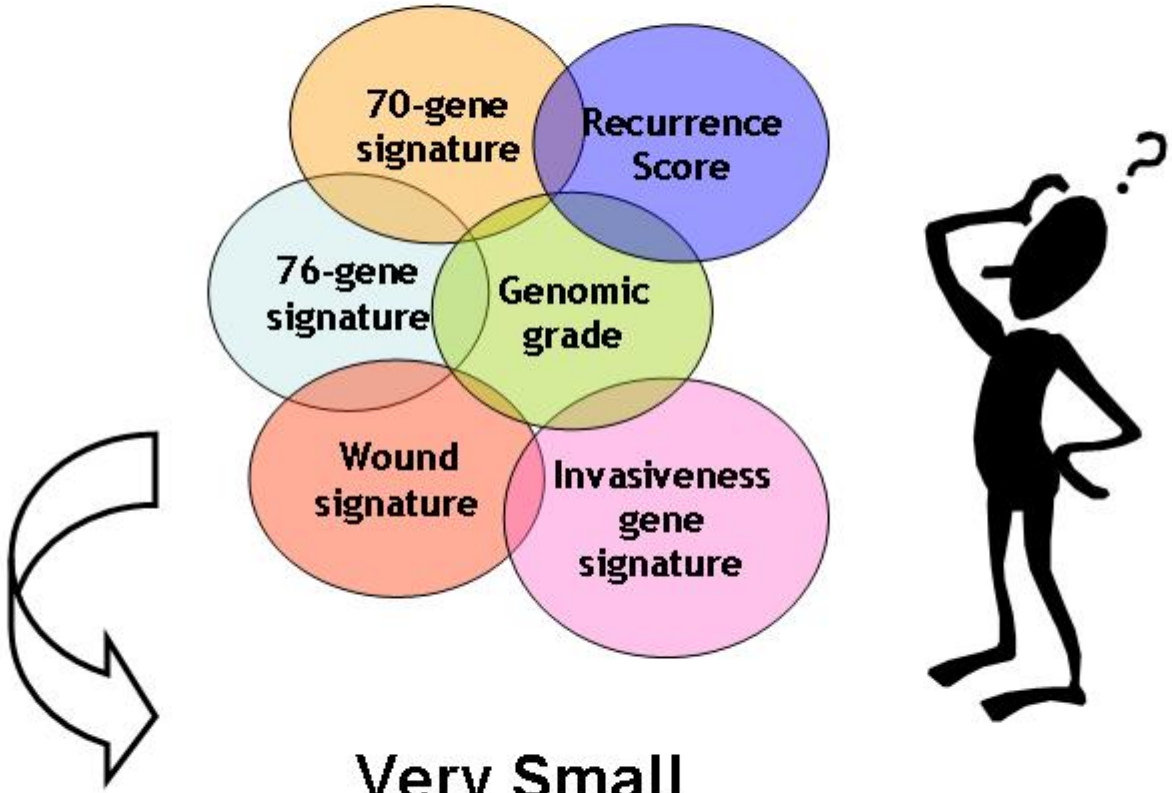
Intermediate Risk : High MGI and low HOXB13/IL17BR

High Risk : High MGI and High HOXB13/IL17BR

Ma et al, CCR 2008

Outcome Signature Genes in Breast Cancer: Is There a Unique Set?

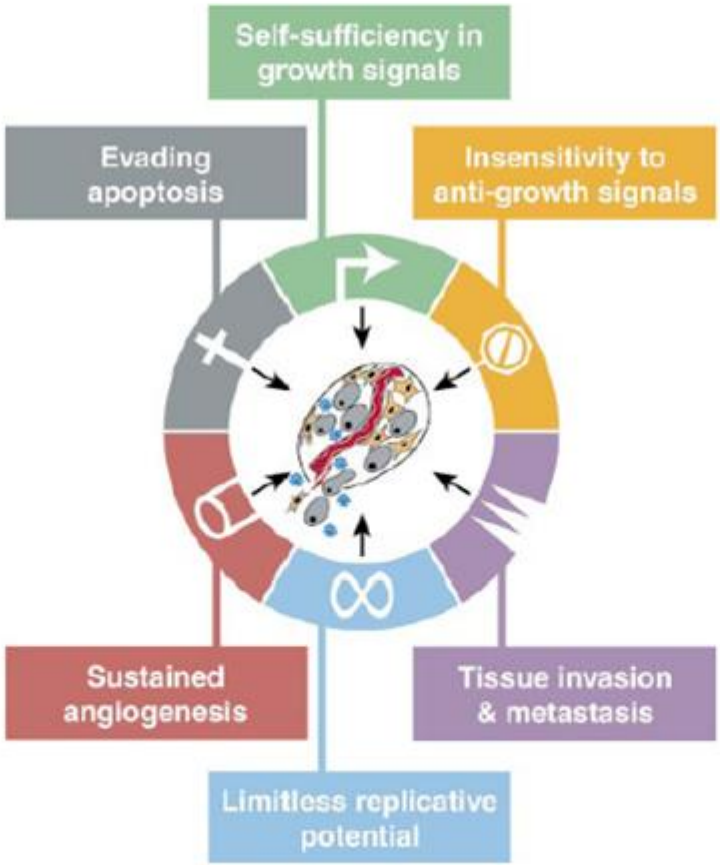
Liat Ein-Dor et al, Bioinformatics, 2004



Very Small Gene Overlap!

META-ANALYSIS
18 studies, N≈3000 pts
Defining biologically relevant Molecular Modules

Hallmarks of breast cancer



Proliferation genes

Immune Response

HER-2 signaling

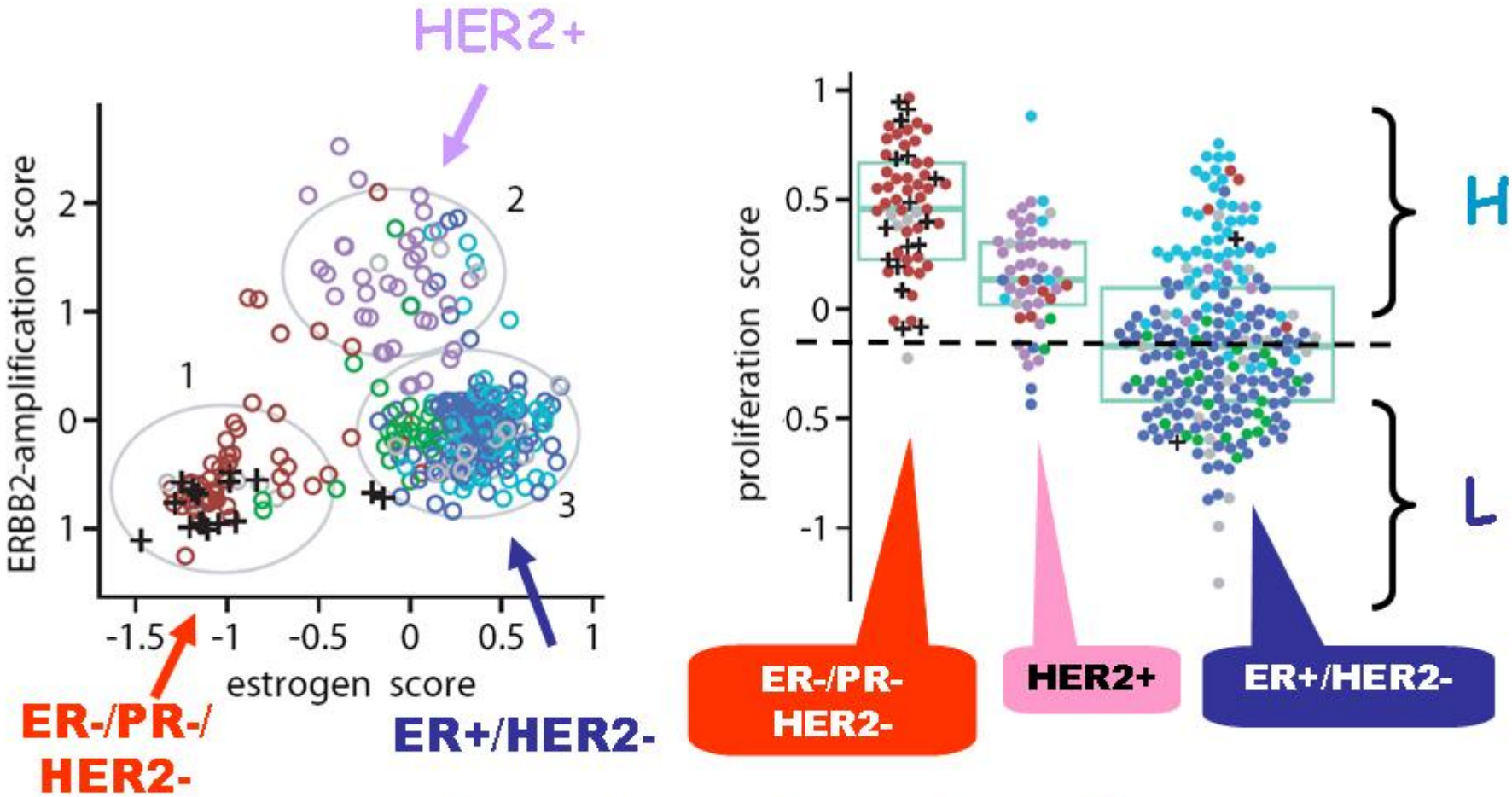
ER signaling

Invasion

Wirapati et al. BCR 2008

Molecular modules divide breast cancers in 4 reproducible subtypes

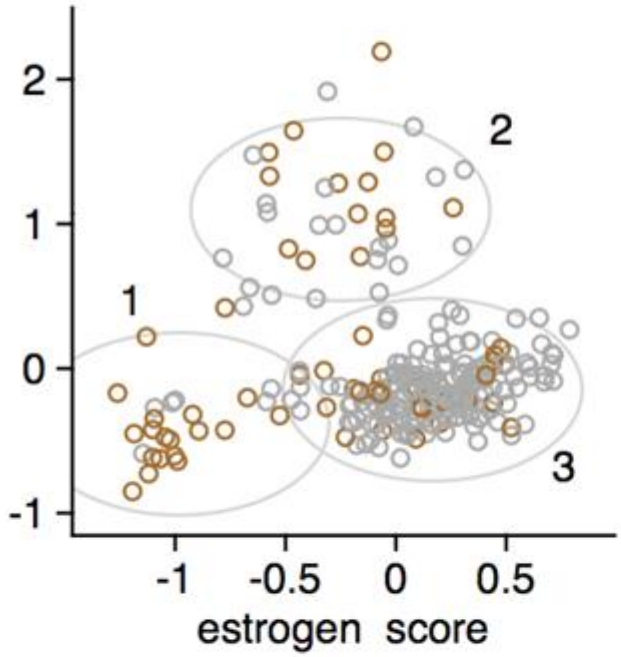
(ER-/HER2-, HER2+, ER+ low, ER+ high proliferation)

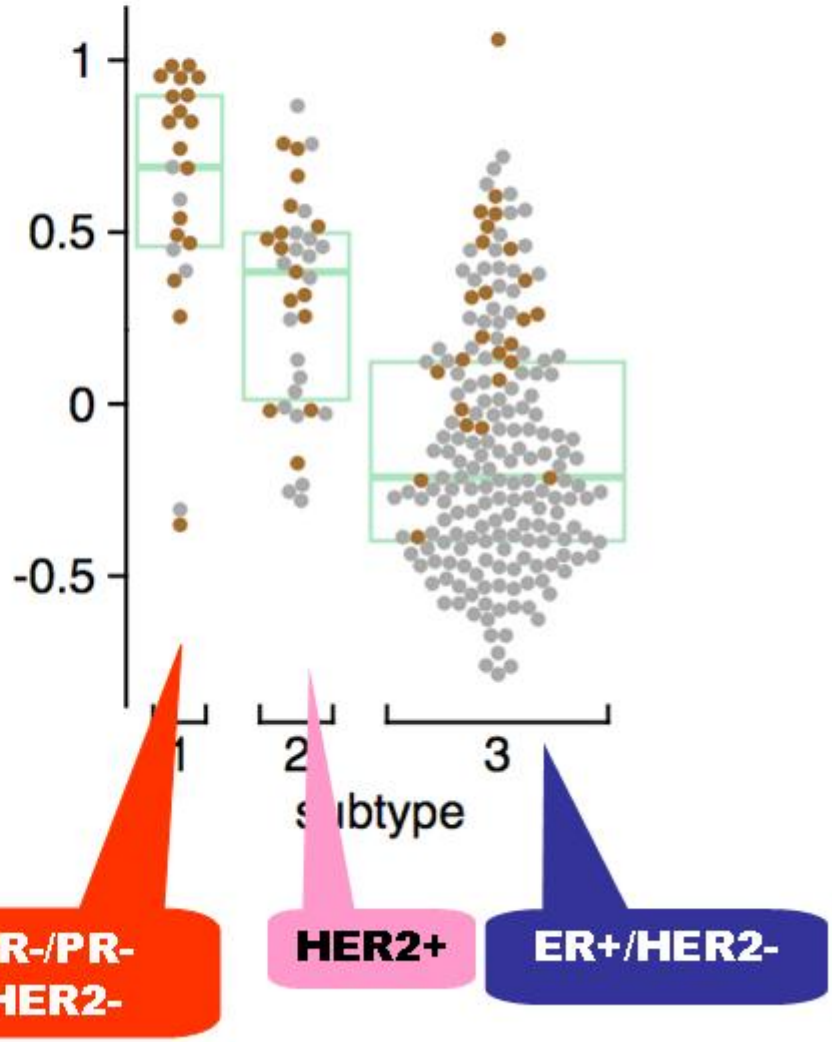


Intrinsic subtype: • basal-like, • her2/neu, • luminal A, • luminal B, • normal-like

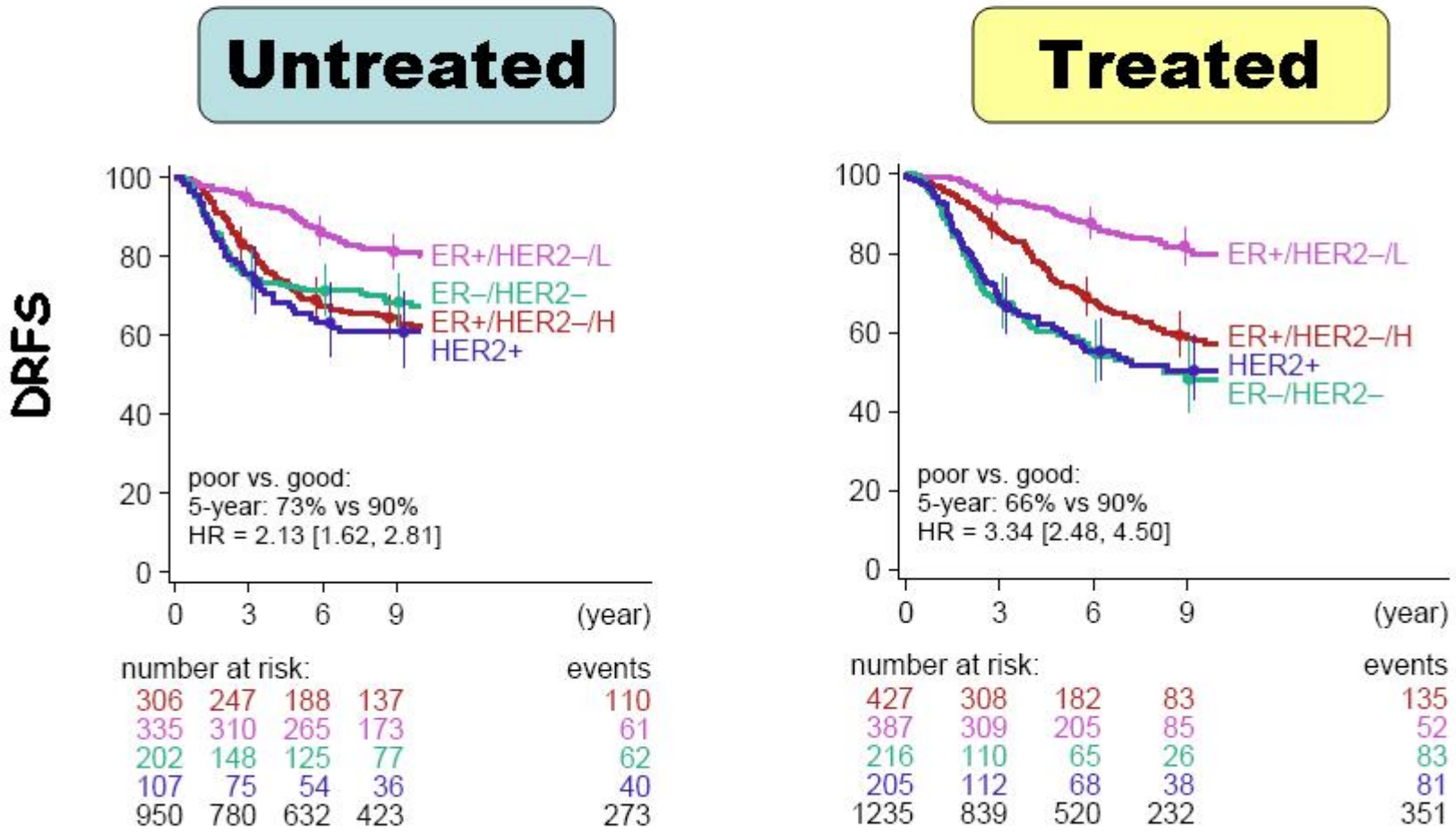
+ = BRCA1 mutation

Molecular Subtypes
P53 Mutation status



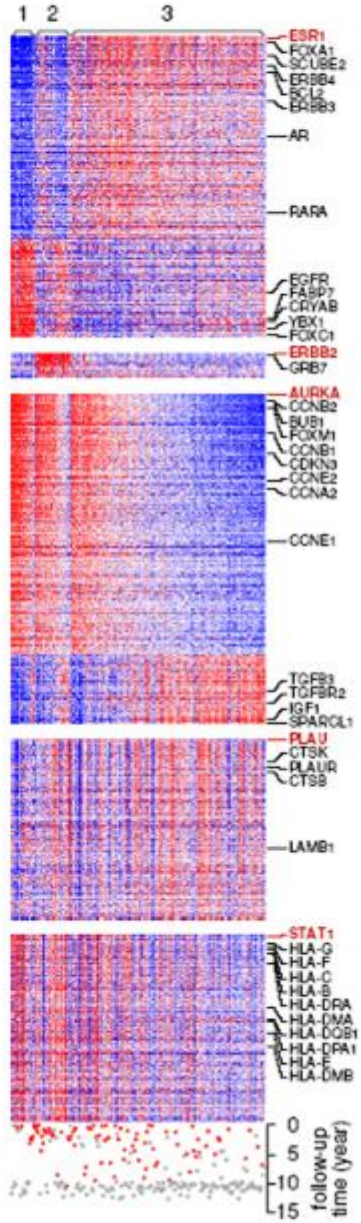


Molecular subtypes and clinical relevance?



Relationship Between Prognostic Signatures and Modular Associations…

9 Gene Expression Signatures



ER-related

HER2-related

Proliferation

Tumor Invasion

Immune response

Dissecting Gene Expression Signatures

9 Prognostic Signatures

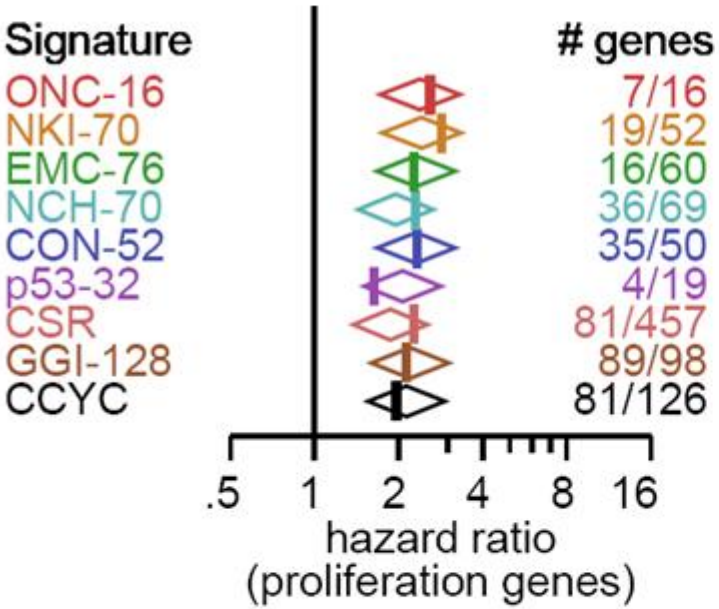
⇩

Two Partial
Prognostic Signatures

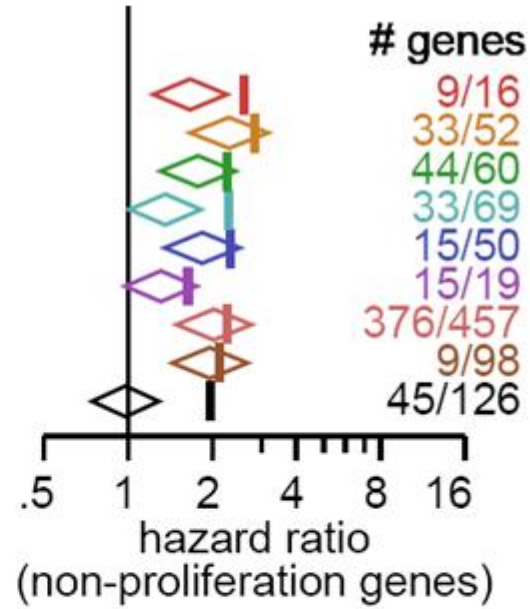
Proliferation Genes	Non-Proliferation Genes

Proliferation=driving force

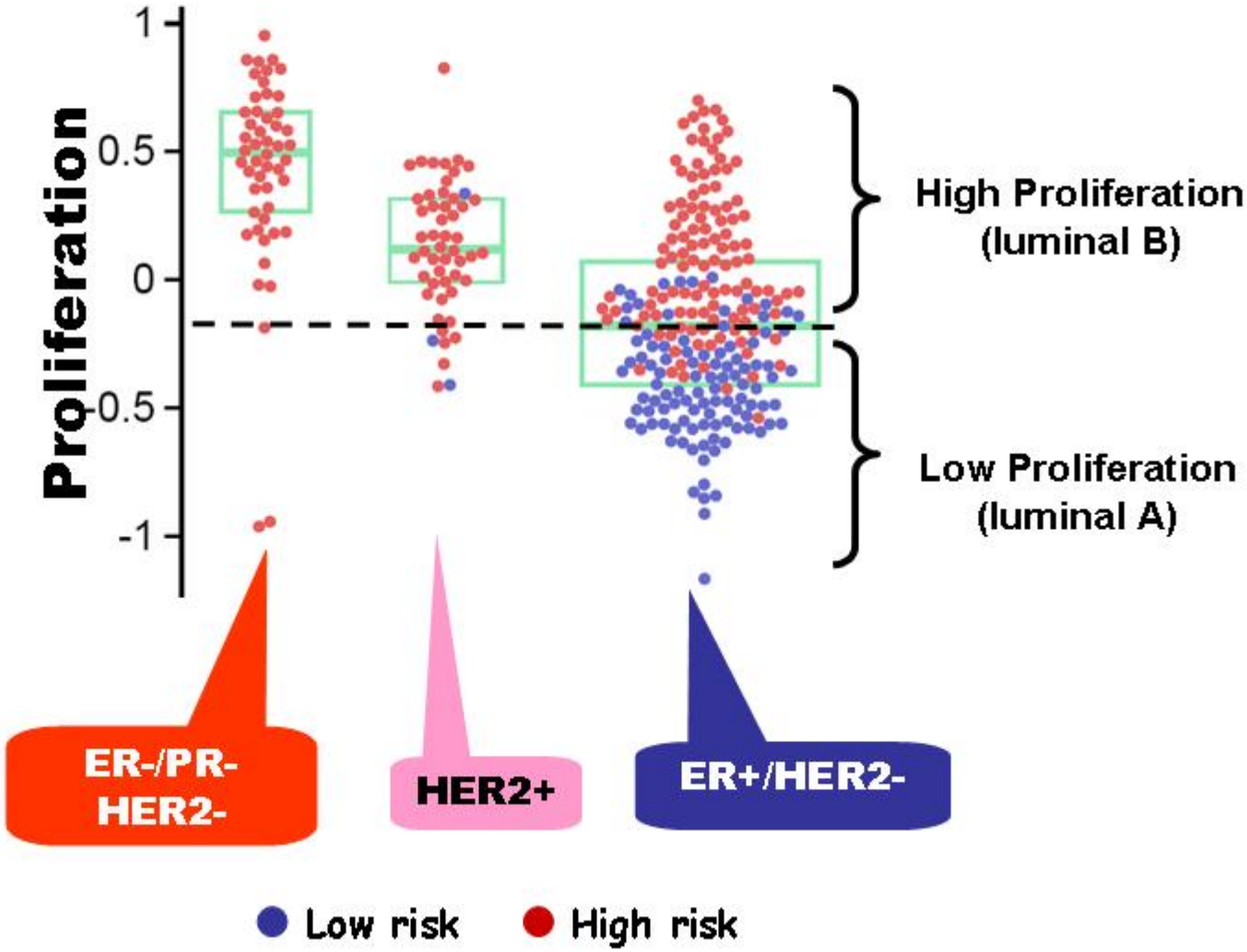
Proliferation Genes

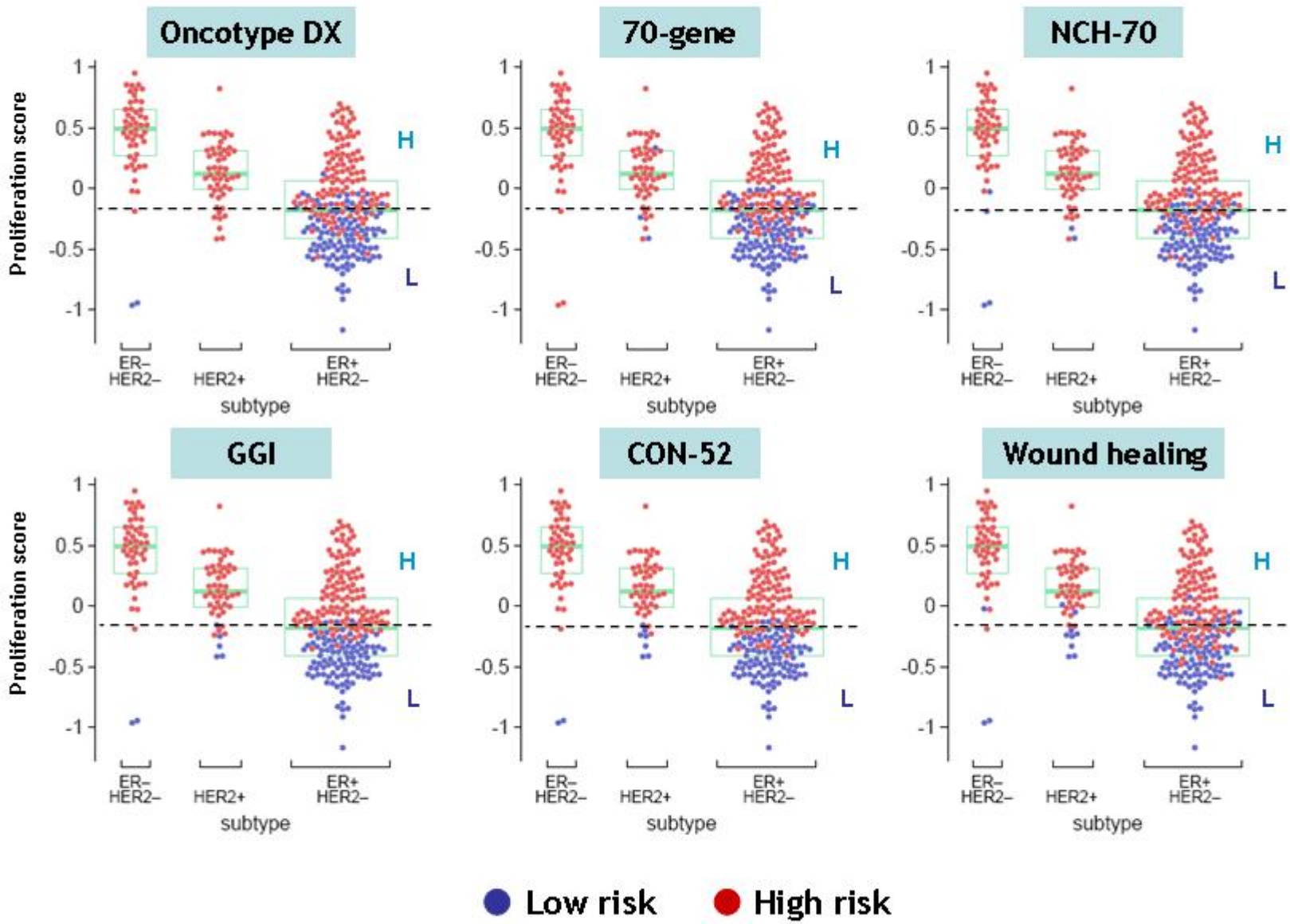


Non-Proliferation Genes



Connection between prognostic signatures, and molecular classification…

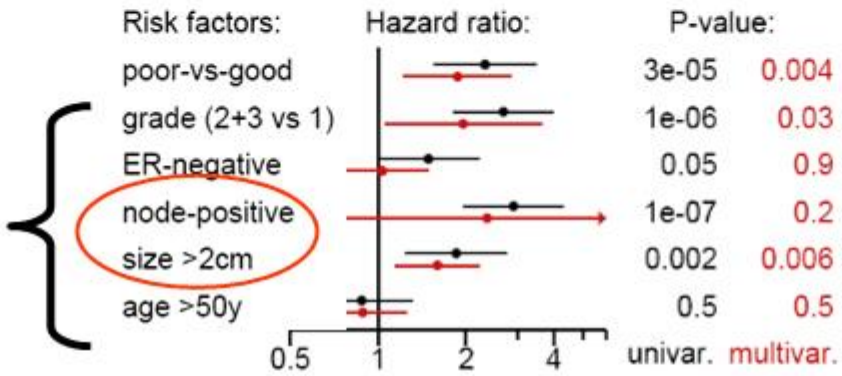



Oncotype DX
70-gene
NCH-70
GGI
CON-52
Wound healing
Proliferation score
1
0.5
0
-0.5
-1
H
L
ER–
HER2–
HER2+
ER+
HER2–
subtype
Low risk
High risk

Clinico-pathological information is still needed!

Genomic

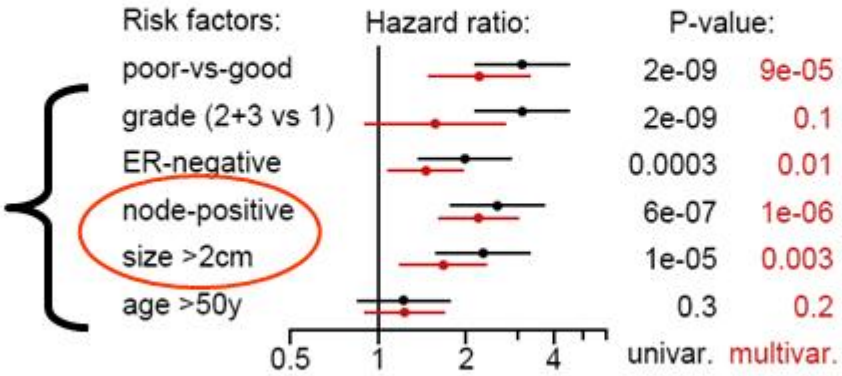
Clinico-pathological



Untreated

Genomic

Clinico-pathological

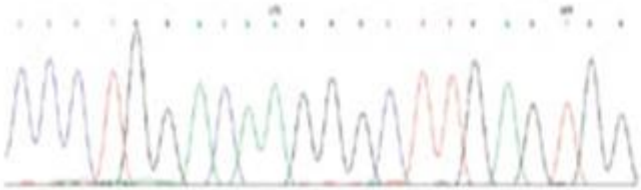


Treated

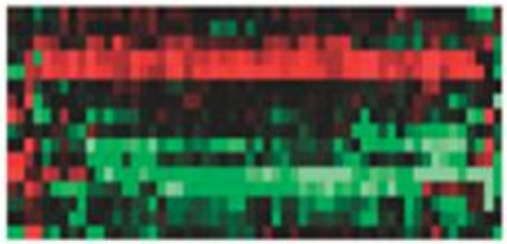
Conclusion

- For the time being pathology cannot be safely replaced by molecular assays
- But we should take the greatest advantage by combining two approaches
- Ultimately one can hope that the molecular classification will be easily translated for clinical daily routine practice by developing IHC assays accordingly.

Proteomics/metabolomics



Genetics/epigenetics



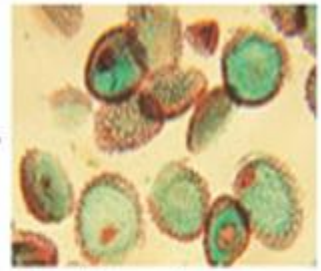
Genomics

Clinical

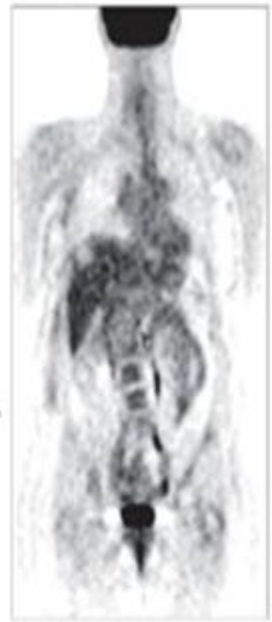
Pathology

Decision-making algorithm

Towards individualized medicine



Circulating and disseminated tumour cells



Modern imaging

Nature Reviews | Cancer