Genomic grade can distinguish ER positive luminal subtypes

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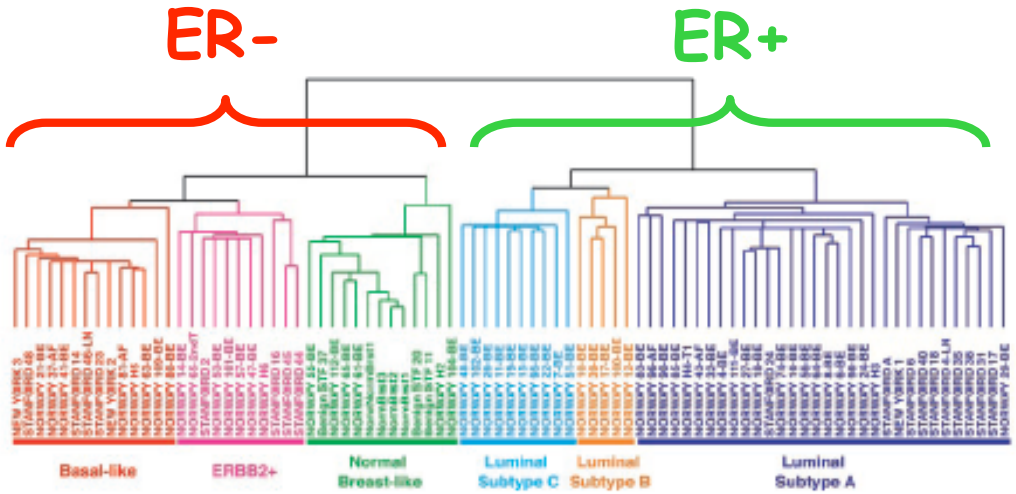
Molecular Classification of Breast Cancer

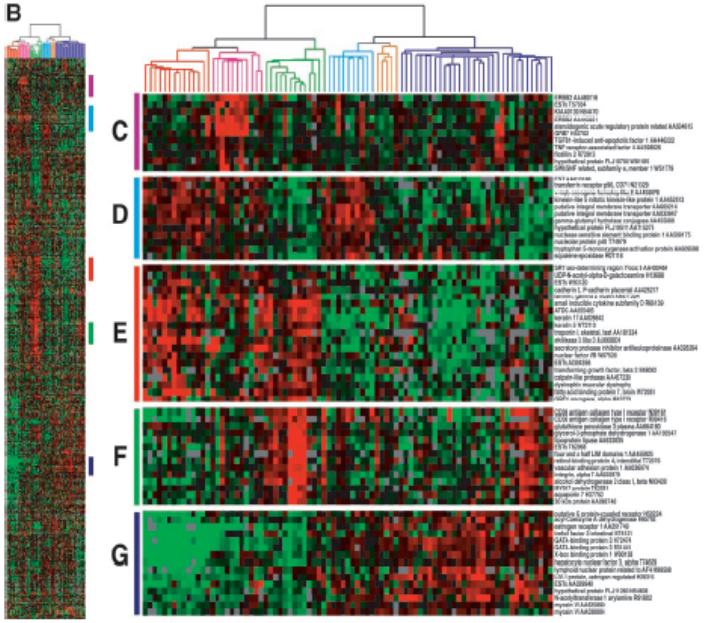


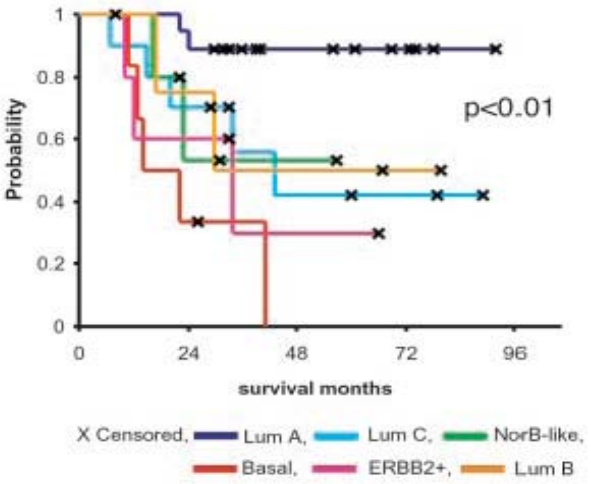
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[i], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

PNAS vol 98, no 19, 10869-10874, 2001

Clinical Outcome





Confirmatory Study

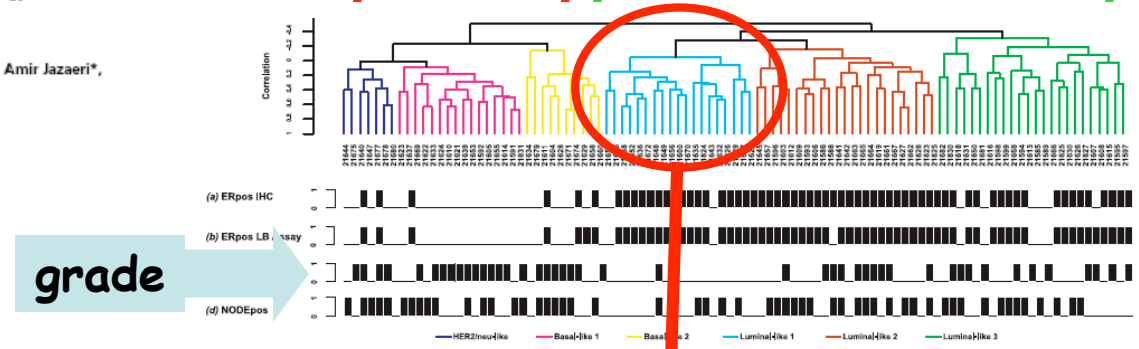
Breast cancer classification and prognosis based on gene expression profiles from a population-based study

Christos Sotiriou*†, Soek-Ying Neo‡, Lisa M. McShane§, Edward L. Korn§, Philip M. Long‡, Amir Jazaeri*, Philippe Martiat†, Steve B. Fox¶, Adrian L. Harris¶, and Edison T. Liu*‖

PNAS vol 100, no 18, 10393–10398, 2003

ER-

ER+



grade

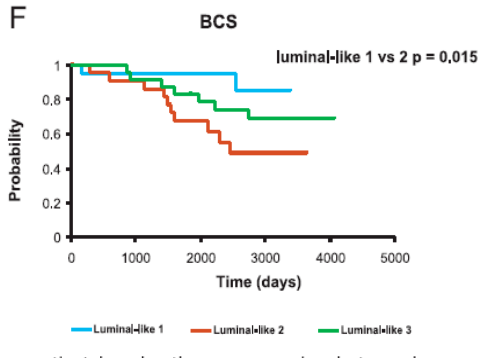
Fig. 1. Dendrogram of 99 breast cancer specimens analyzed by hierarchical clustering analysis using 706 probe elements selected for the high variability across all tumors (see *Materials and Methods*). The tumors were separated into two main groups mainly associated with ER status as determined by the ligand-binding (LB) assay and confirmed by immunohistochemistry (IHC). The dendrogram further branched into smaller subgroups within the ER+ and ER− classes based on their basal and luminal characteristics: Her-2/neu subgroup, dark blue; basal-like 1 subgroup, pink; basal-like 2 subgroup, yellow; luminal-like 1 subgroup, light blue; luminal-like 2 subgroup, red; and luminal-like 3 subgroup, green. Black bars represent ER+ tumors assessed by IHC (*a*), ER+ tumors assessed by LB assay (*b*), grade 3 (*c*), and node-positive tumors (*d*).

Table 1. No. of genes discriminating known clinico-pathological phenotypes in breast cancer

Clinico-pathological parameters	No. of significant expressed genes, $P < 0.001$*
ER status	
ER+ versus ER−	606
Grade status	
Grade 1/2 versus grade 3	137
Node status	
Node positive versus negative	11
Tumor size	
≤2 cm versus >2 cm	3
Menopausal status	
Premenopausal versus postmenopausal	13

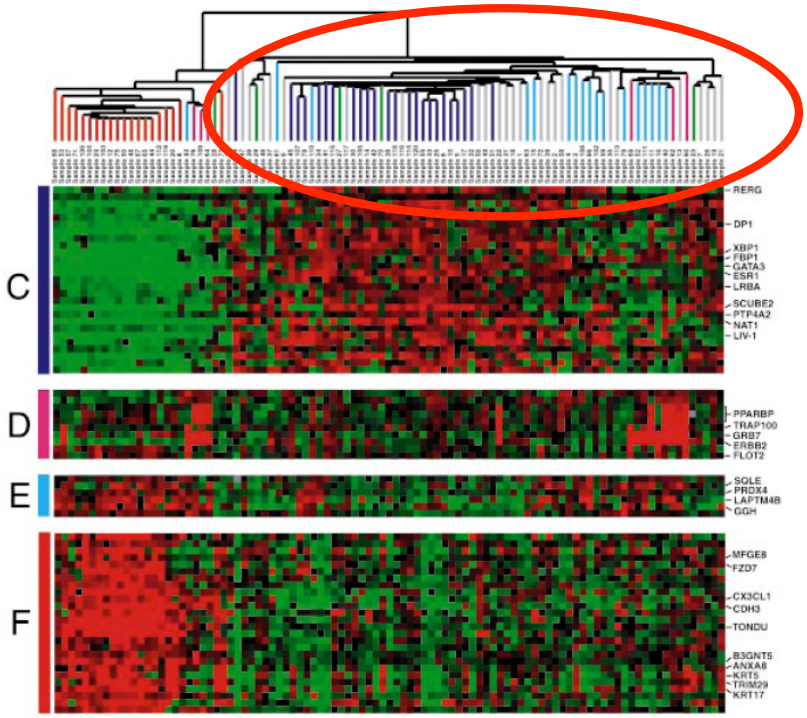
*For 7,650 comparisons, the expected number of spuriously significant (false positive) findings at level $P < 0.001$ is ≈8 or less.

Clinical Outcome

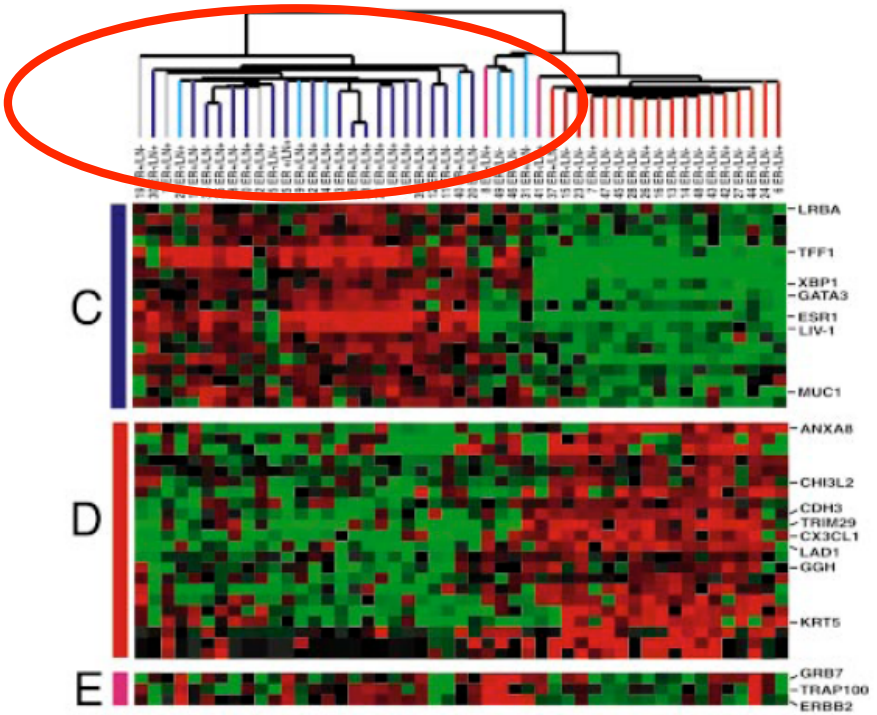


Definition of luminal subtypes has been inconsistent between published series …

Van't veer *et al.* data set



West *et al.* data set



Luminal *A*

Luminal B

PNAS vol 100, no 14, 8418-8423, 2003

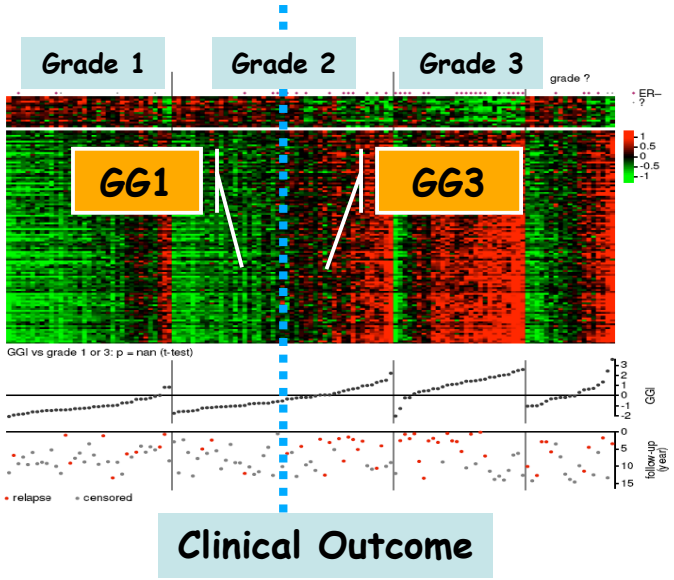
Defining Genomic Grade in Breast Carcinoma
ASCO 2005

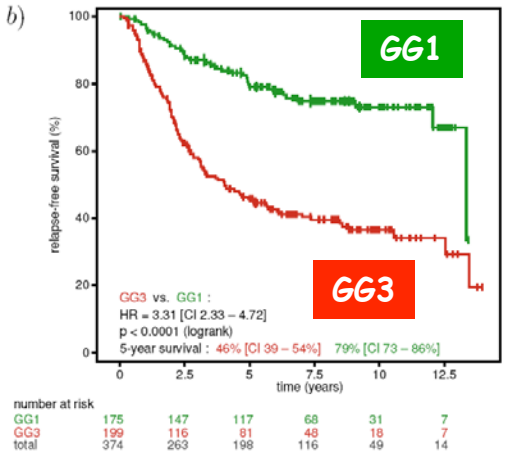
128 probe sets of "genomic grade" (97 genes) FDC>0

UBE2C RACGAP1 C10orf3 KPNA2
PTTG1 KIF4A TPX2 FOXM1 KIF20A STK6
STK6 DLG7 DDX39 MELK CCNA2 MYBL2
KIAA0186 BIRC5 NUDT1 KPNA2 KIF2C
KIFC1 SPAG5 ASPM CDC20 FEN1
TIMELESS ESPL1 CENPA MCM2
DONSON CDC2 CCNB1 CDCA8 KIF11
DKFZp762E1312 MCM10 CDKN3 MARS
CENPA CCNB2 TRIP13 LMNB1 CDC2
TROAP AURKB FLJ20641 BUB1B CENPE
CCNE2 CDC2 FSHPRH1 BRRN1 HMMR
POLQ PMSCL1 MKI67 GTSE1 ZWINT
GMPS TMPO RRM2 KLIP1 FEN1 MKI67
KIF2C PLK1 BLM BUB1 LOC146909 OIP5
K-ALPHA-1 SHMT2 DC13 H2AFZ MCM4
UBE2S TUBA6 TTK FLJ10156 C20orf24
MARS RRM2 MKI67 CENPF PRC1
BM039 K-ALPHA-1 CDC25A NUSAP1
KNTC2 EXO1 MCM4 BIRC5 MAD2L1
UBE2N MGC5528 CDK2 ESPL1 HCAP-G
CCT5 SLC7A5 CDCA3 ORMDL2 KIF14
PTDSR K-ALPHA-1 BIRC5 RNASEH2A
HIST1H4B HMGB3 NEK2 KNSL7 SNRPC
MKI67 EZH2 DNAJC9 DC12 TPRT
COX7B MRPS17 SIL FBXO5 HCAP-G
HN1 POLR2K NUTF2 MCM6 MCM4 VRK1
PKMYT1 RAD51 ...

$$GGI = scale\left[\sum_{j\in G_3} x_j - \sum_{j\in G_1} x_j - cutoff\right]$$

Define GGI score (Gene-expression Grade Index)





(JNCI *in press*)

Aims

- To determine if Genomic Grade can better define luminal subtypes in breast carcinoma

- To correlate these subtypes with clinical outcome

Methods

Original Datasets ER+

Untreated

- Oxford
- Karolinska

N=86

Tamoxifen-Treated

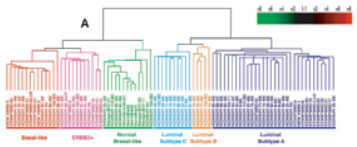
- Oxford
- Karolinska
- Guys

N=249

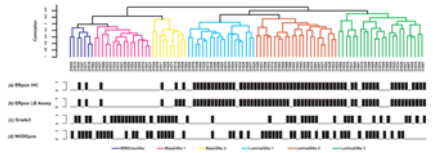
Affymetrix U133A
22,283 probe sets

Published datasets

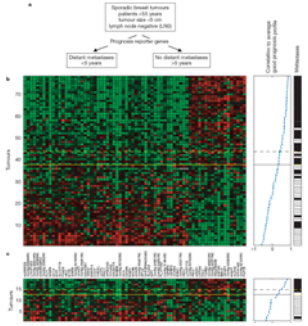
Sorlie *et al.*
PNAS, 2001



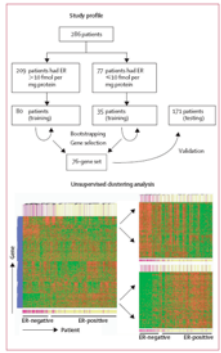
Sotiriou *et al.*
PNAS, 2003



Van de Vijver *et al.*
NEJM, 2002



Wang Y *et al.*
The Lancet, 2005



Total Number ER+/luminal subtypes = **787 samples**

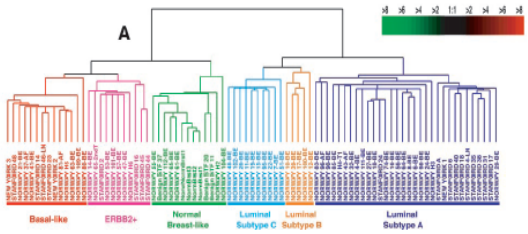
Results

Applying Genomic Grade to Molecular Subtypes

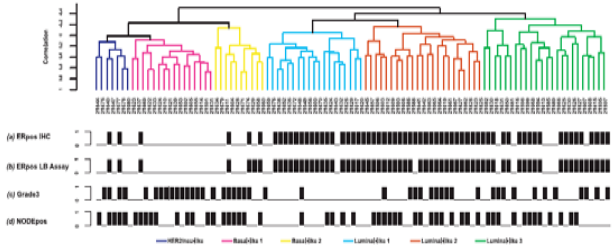
$$GGI = scale\left[\sum_{j\in G_3} x_j - \sum_{j\in G_1} x_j - cutoff\right]$$

GGI score (Gene-expression Grade Index)

Sorlie *et al.* PNAS, 2001

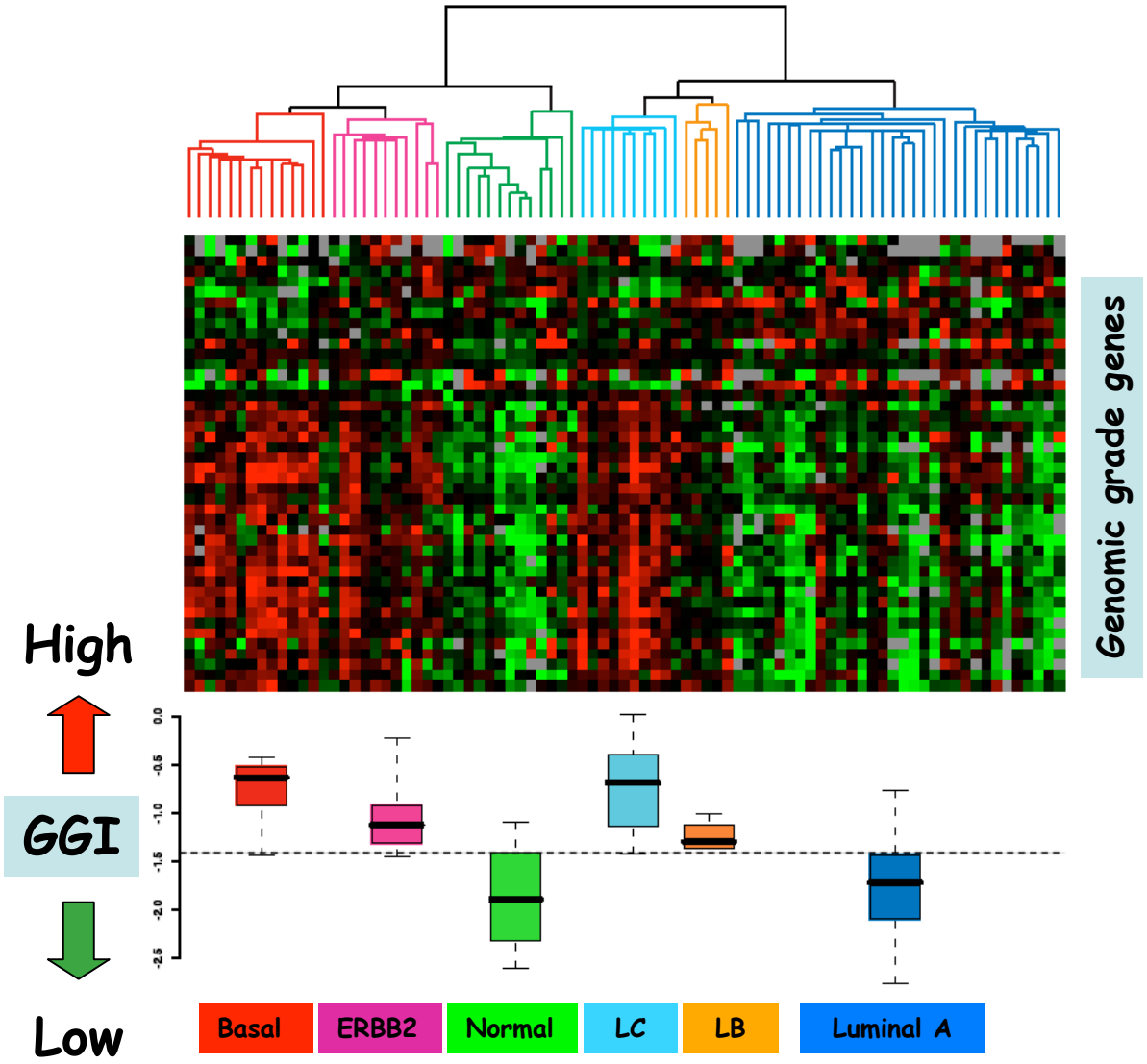


Sotiriou *et al.* PNAS, 2003

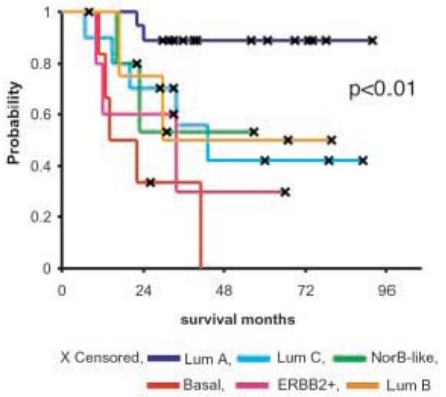


Applying Genomic Grade to Molecular Subtypes

Sorlie *et al.* PNAS 2001

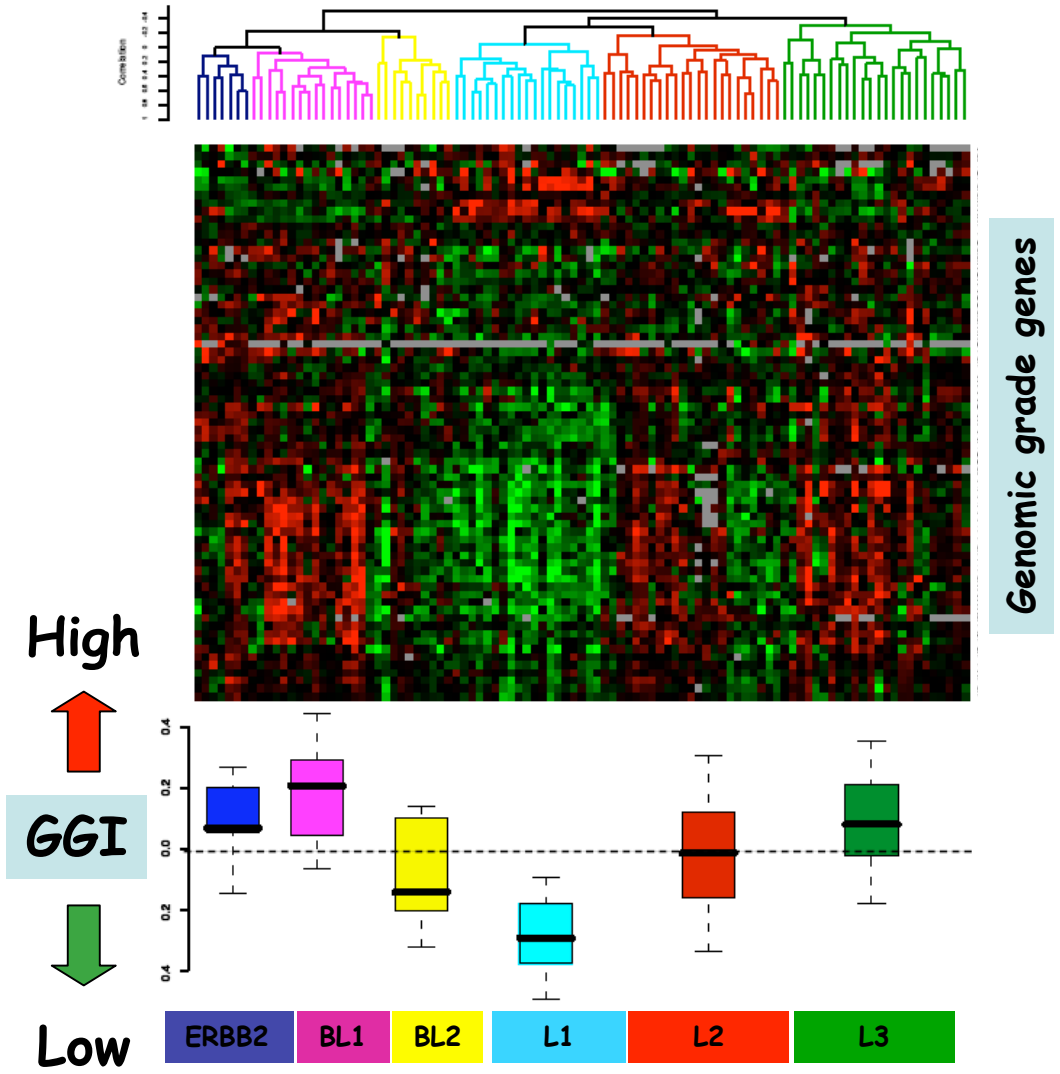


Clinical Outcome

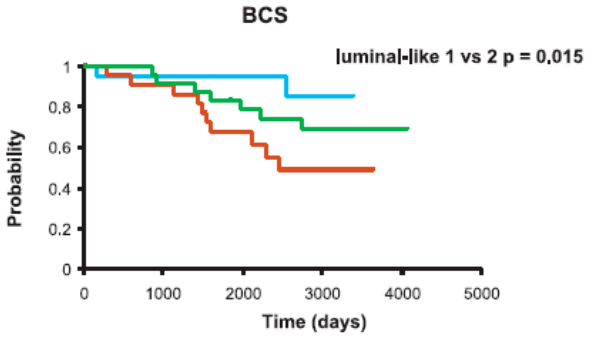


Applying Genomic Grade to Molecular Subtypes

Sotiriou *et al.* PNAS 2003

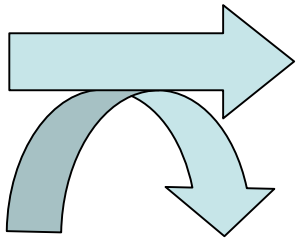


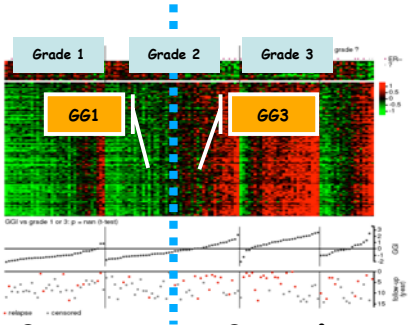
Clinical Outcome



Clinical relevance of ER-positive luminal subtypes as defined by Genomic Grade

ER Positive Tumors





Genomic Grade

Clinical Relevance?

Genomic Grade Subtypes

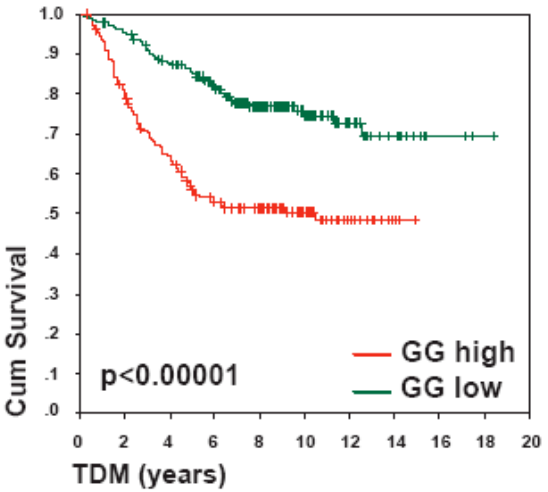
>

Quantitative Levels of ER and PgR?

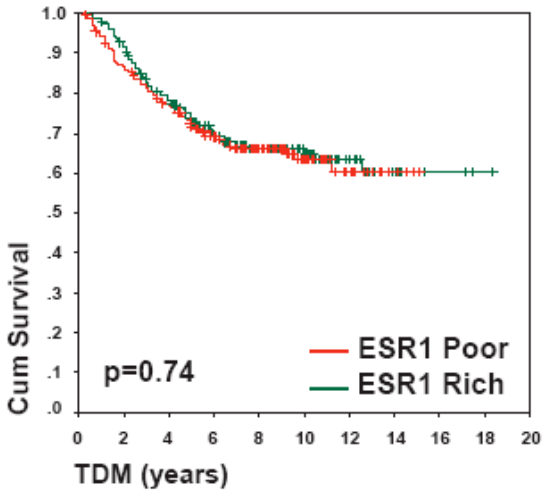
Time to Distant Metastases
GG, ER and PgR expression levels

ER+ UNTREATED POPULATION N = 417

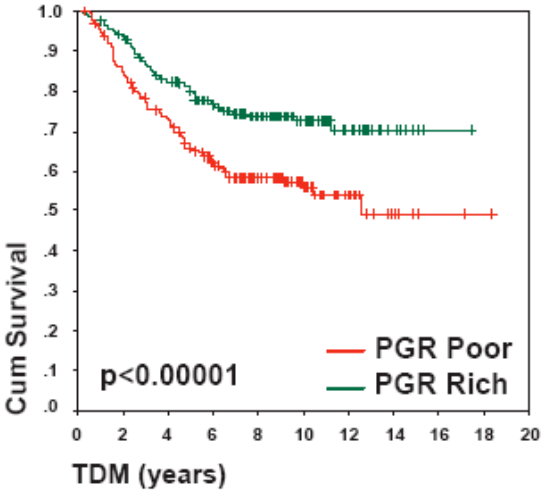
GG



ER



PgR

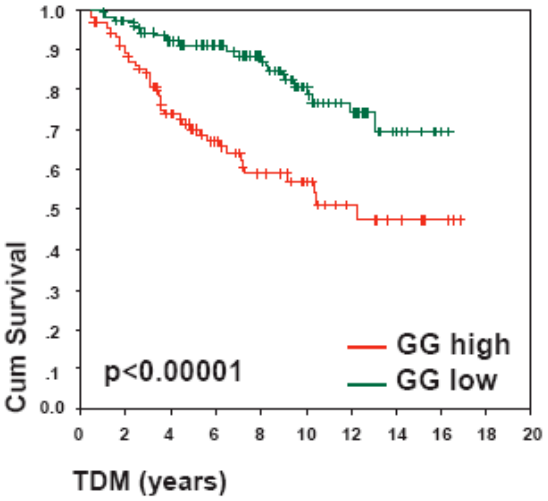


ER and PgR cutoff = Median Expression level

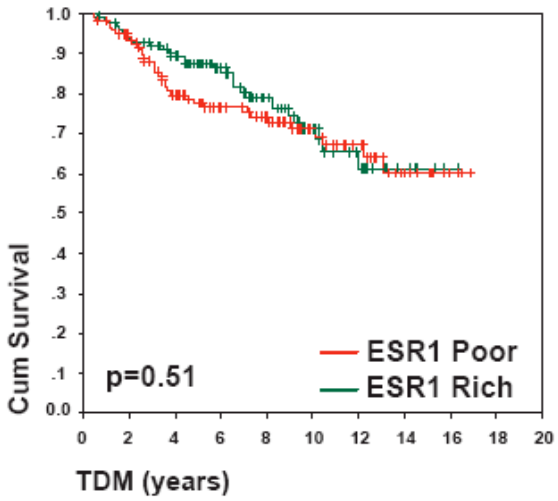
Time to Distant Metastases
GG, ER and PgR expression levels

ER+ TAMOXIFEN-TREATED N = 249

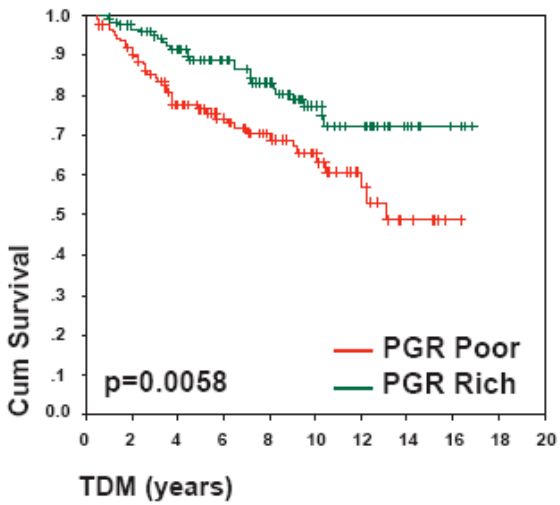
GG



ER



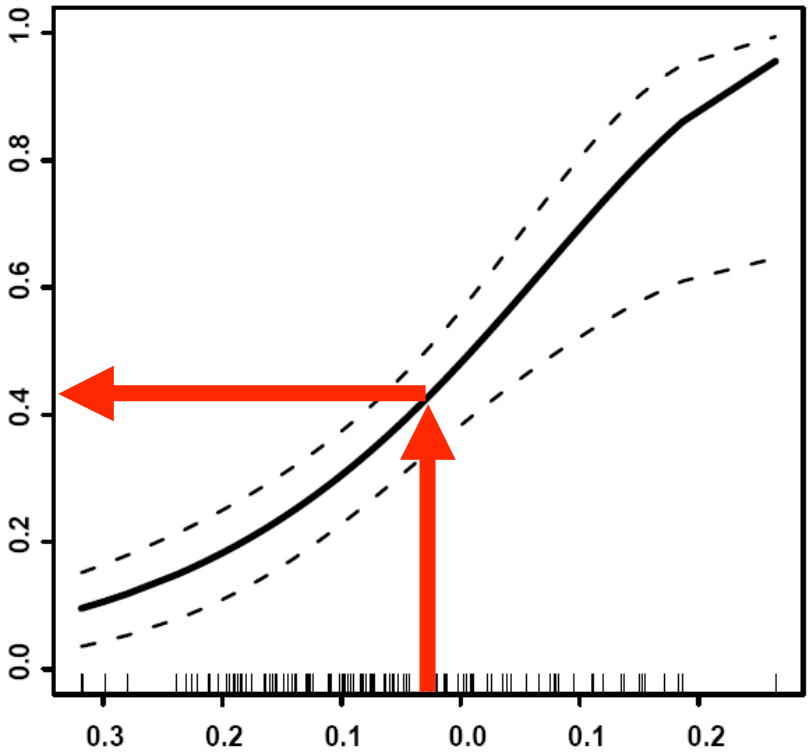
PgR



ER and PgR cutoff = Median Expression level

Expected Rate of Developing Distant Metastases at 10 Years

% Distant Metastases



GGI

ER mRNA levels

PgR mRNA levels

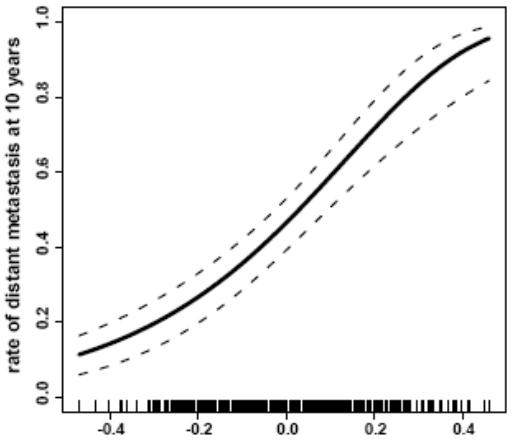
Low ⟺ High

parameter

Rate of Distant Metastases at 10 years based on the GGI, ER and PgR expression levels

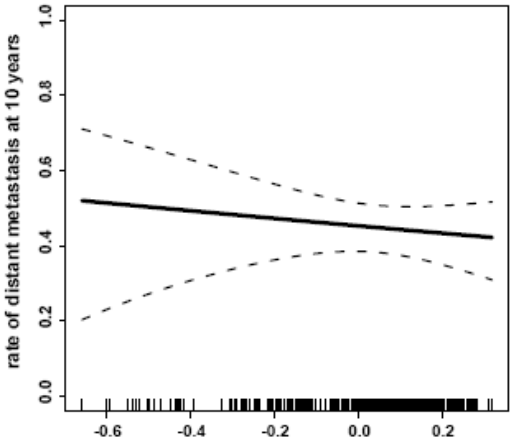
ER+ UNTREATED POPULATION N = 417

GGI



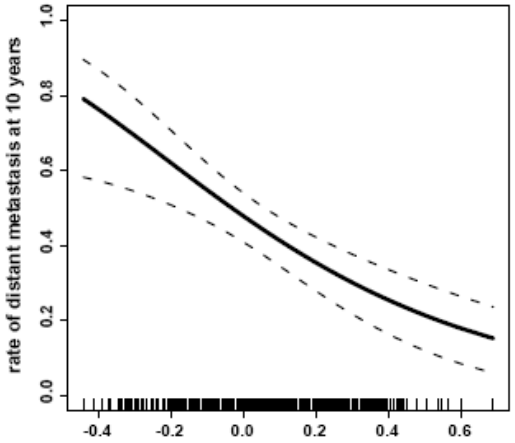
Low ⟷ High

ER



Poor ⟷ Rich

PgR

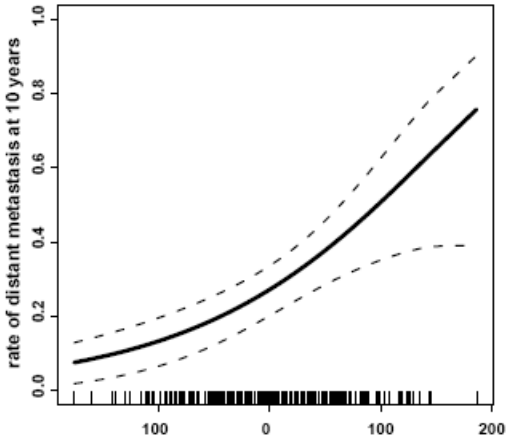


Poor ⟷ Rich

Rate of Distant Metastases at 10 years based on the GGI, ER and PgR expression levels

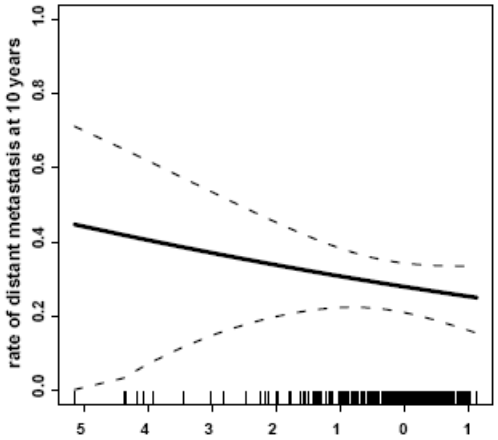
ER+ TAMOXIFEN-TREATED N = 249

GGI



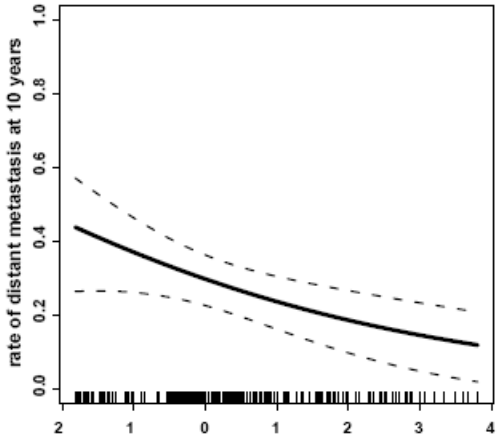
Low ⟷ High

ER



Poor ⟷ Rich

PgR



Poor ⟷ Rich

Prognostic Value of GG in Multivariate Model

ER+ UNTREATED POPULATION N = 417

	Univariate		Multivariate	
	Hazard ratio (95%CI)	***p*¶**	**Hazard ratio (95%CI)**	***p*¶**
Age (years) ≤ 50 vs >50	1.1 (0.6-2.0)	0.9	0.9 (0.4-1.9)	0.8
Size >2cm vs ≤ 2cm	2.7 (1.6-4.5)	**$1x10^{-3}$**	2.1 (1.2-3.8)	**$7x10^{-2}$**
Histological grade 1 vs 2 vs 3	2.1 (1.5-3.0)	**$8x10^{-4}$**	1.4 (0.9-2.1)	0.1
ER Rich vs Poor	0.9 (0.7-1.3)	0.9	1.2 (0.7-2.2)	0.5
PgR Rich vs Poor	0.5 (0.4-0.7)	**$3x10^{-3}$**	0.8 (0.4-1.3)	0.3
Genomic Grade High vs Low	2.6 (1.8-3.7)	**$1x10^{-6}$**	2.3 (1.2-4.2)	**$8x10^{-2}$**

Prognostic Value of GG in Multivariate Model

ER+ TAMOXIFEN-TREATED N = 246

	Univariate		Multivariate	
	Hazard ratio (95%CI)	***p*¶**	**Hazard ratio (95%CI)**	***p*¶**
Age (years) ≤ 50 vs >50	0.9 (0.3-2.6)	0.9	0.8 (0.2-2.9)	0.7
Size >2cm vs ≤ 2cm	2.0 (1.1-3.5)	**$1x10^{-1}$**	1.7 (0.9-3.3)	0.1
Histological grade 1 vs 2 vs 3	1.7 (1.1-2.6)	**$1x10^{-1}$**	1.1 (0.6-1.8)	0.8
Nodal status Positive vs Negative	1.4 (0.8-2.5)	0.2	1.1 (0.6-2.0)	0.9
ER Rich vs Poor	0.8 (0.5-1.4)	0.5	0.9 (0.5-1.8)	0.9
PgR Rich vs Poor	0.5 (0.3-0.8)	**$5x10^{-4}$**	0.7 (0.4-1.4)	0.4
Genomic Grade High vs Low	3.1 (1.9-5.2)	**$<1x10^{-5}$**	2.1 (1.0-4.4)	**$3x10^{-3}$**

Conclusions (1)

- The use of Genomic Grade can distinguish two luminal subtypes in a highly reproducible manner across multiple datasets and microarray platforms.

- Genomic Grade-defined subtypes show statistically distinct clinical outcome in both untreated and tamoxifen-treated populations.

Conclusions (2)

- These subtypes may provide important stratification for future breast cancer trials and hence have the potential to individualize treatment.

- Further biological investigations into these phenotypes may result in identifying important therapeutic targets.

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  London UK
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  Cheryl Gillett, Kenneth Ryder,
  Tony Ng,

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Backup

BACKGROUND

- Several microarray studies have shown that breast tumours can be grouped in at least 5 to 6 different molecular subtypes namely basal-like, erbB2-like, normal-like and luminal-like subtypes with distinct clinical outcome.

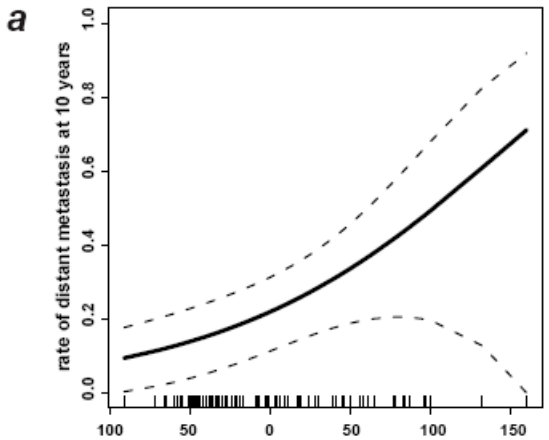
- Although the basal and the erbB2 subtypes are repeatedly recognized as distinct entities, the definition of luminal subtypes has been far from consistent between published series.

- Refinement of their molecular definition is therefore needed.

Rate of Distant Metastases at 10 years based on the GGI, ER and PgR expression levels

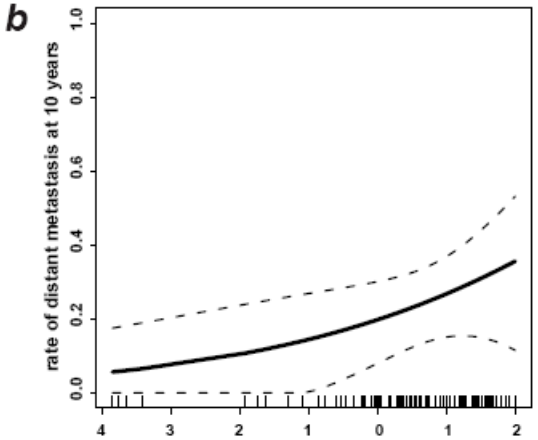
ER+ UNTREATED POPULATION N = 86

GGI



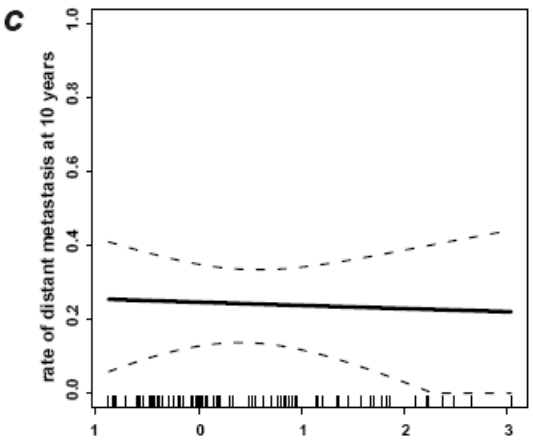
Low ⟷ High

ER



Poor ⟷ Rich

PgR

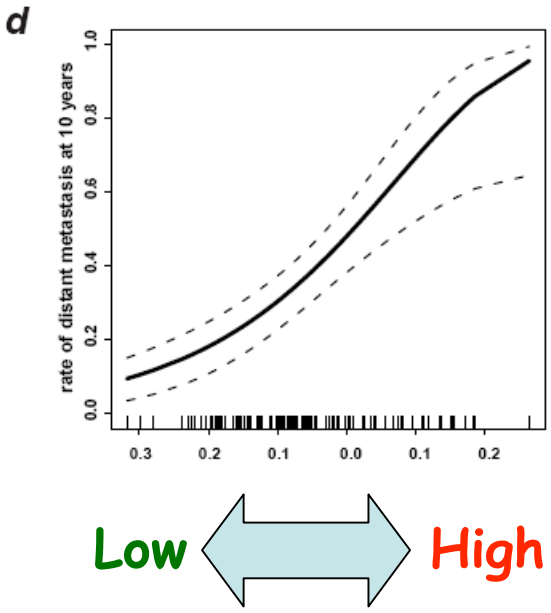


Poor ⟷ Rich

Rate of Distant Metastases at 10 years based on the GGI, ER and PgR expression levels

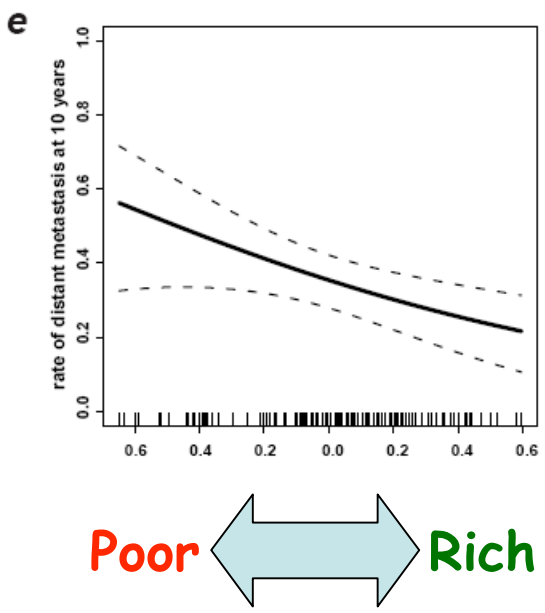
ER+ Van de Vijver *et al.* NEJM N = 122

GGI



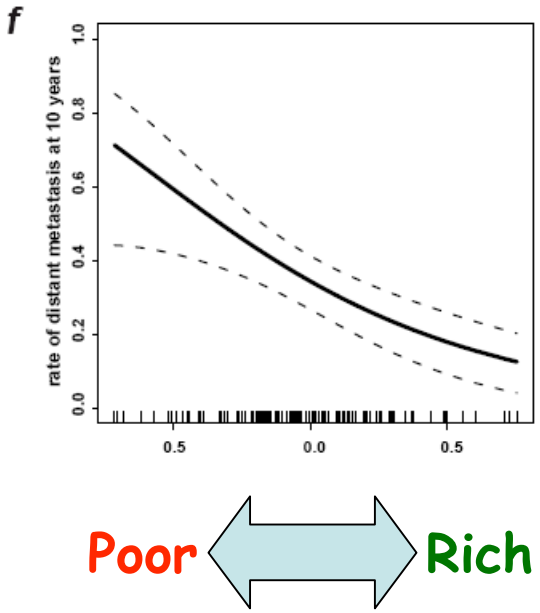
Low ⟷ High

ER



Poor ⟷ Rich

PgR

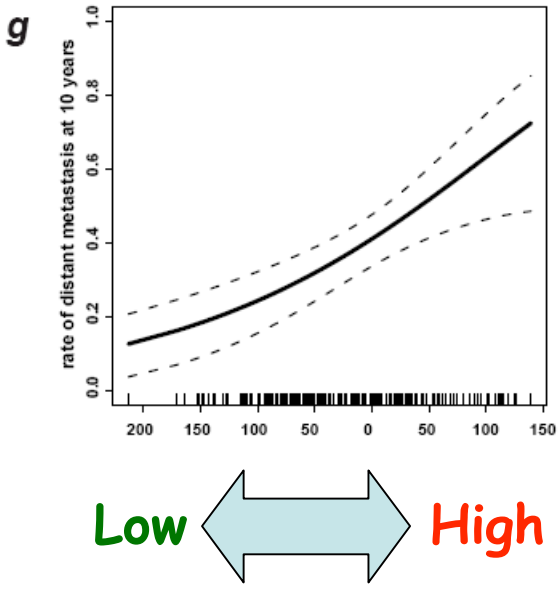


Poor ⟷ Rich

Rate of Distant Metastases at 10 years based on the GGI, ER and PgR expression levels

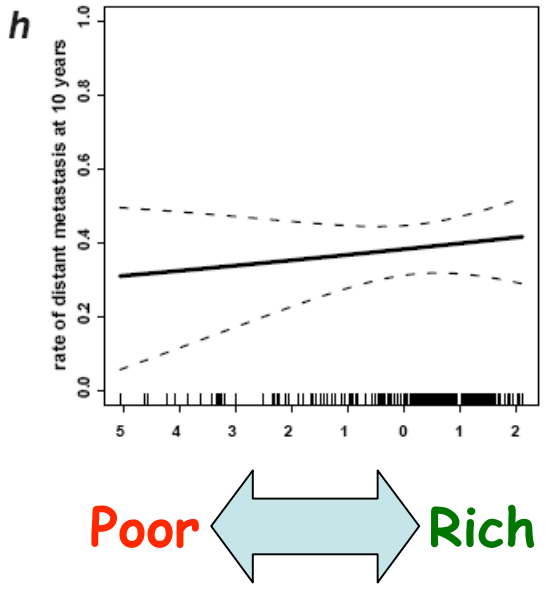
ER+ Wang Y *et al.* The Lancet N = 209

GGI



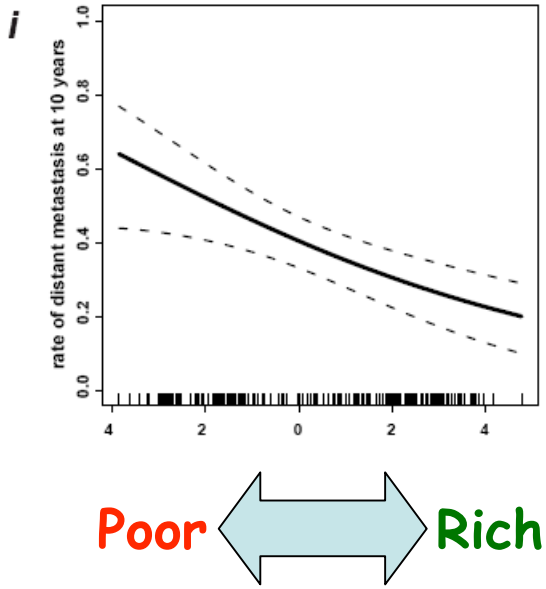
Low ⟷ High

ER



Poor ⟷ Rich

PgR



Poor ⟷ Rich

Multigene Predictors of Clinical Outcome in Hormone Receptor Positive B.C.

	ONCOTYPE DX	GGI
Patient population	Node -	Node – and +
Core genes	Proliferation/ER/ HER2/invasion	Proliferation/ differentiation
Key findings	ER alone<PgR<**RS**	ER alone<PgR<**GGI**

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