Is genomic grading killing histological grading?

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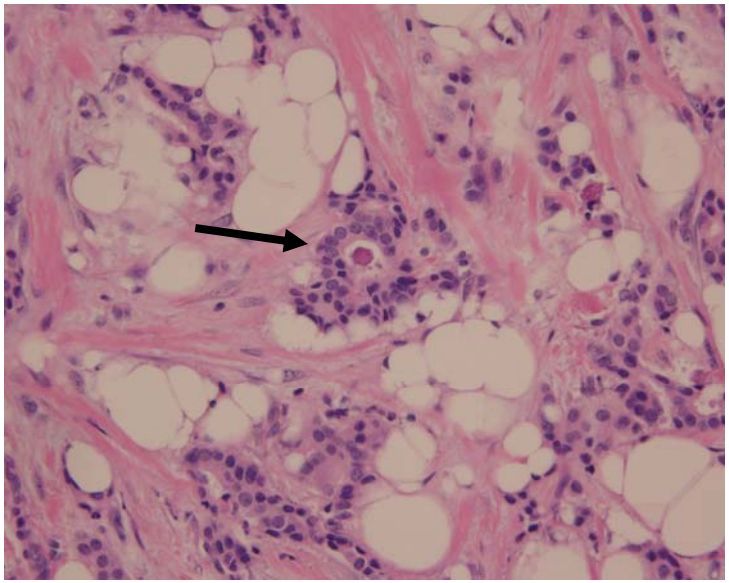
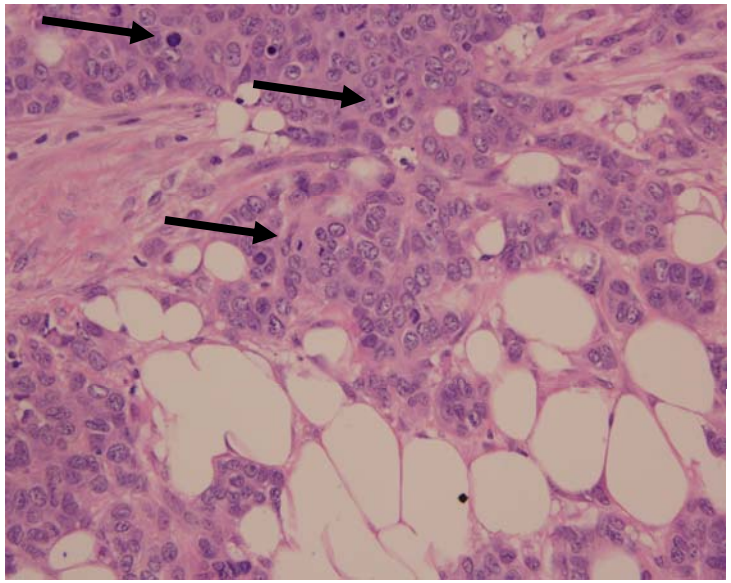
Histological Grade and Breast Cancer Biology
PHENOTYPE

Low Grade



Polarized groups of cells
that form tubular
or duct-like structures

High Grade



·No tubular structures
·Nuclear pleomorphism
·Mitotic activity+++

Histological Grade and Breast Cancer Biology
PATTERN of TUMOR MARKERS

Low Grade

Positively correlated to ER + status:

- PGR
- TFF1
- CDH1
- DSP
- MDM2
- NME1
- CCND1
- TJP1...

High Grade

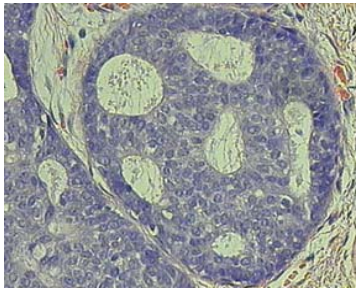
Positively correlated to ER - status:

- CDKN2A
- CCNE
- EGFR
- ERBB2
- SERPINE1
- PLAU
- HXB
- CDH3...

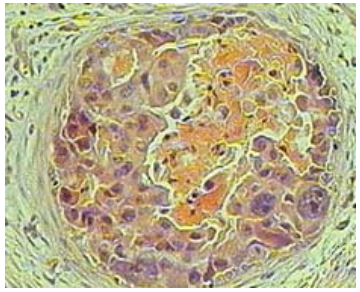
Lacroix et al, ERC 2004

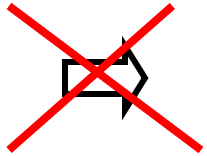
Histological Grade and Breast Cancer PROGRESSION

Low Grade DCIS

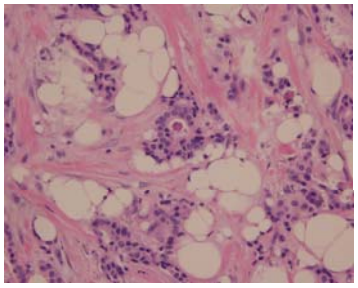


High Grade DCIS

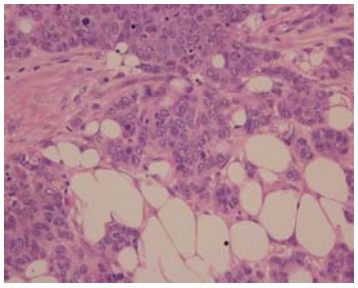




Low Grade DC



High Grade DC



Tumor Markers:
p53, erbb2, Ki-67, ER, PR, bcl-2, angiogenesis

- No marker was clearly associated with progression
- Correlation with grade

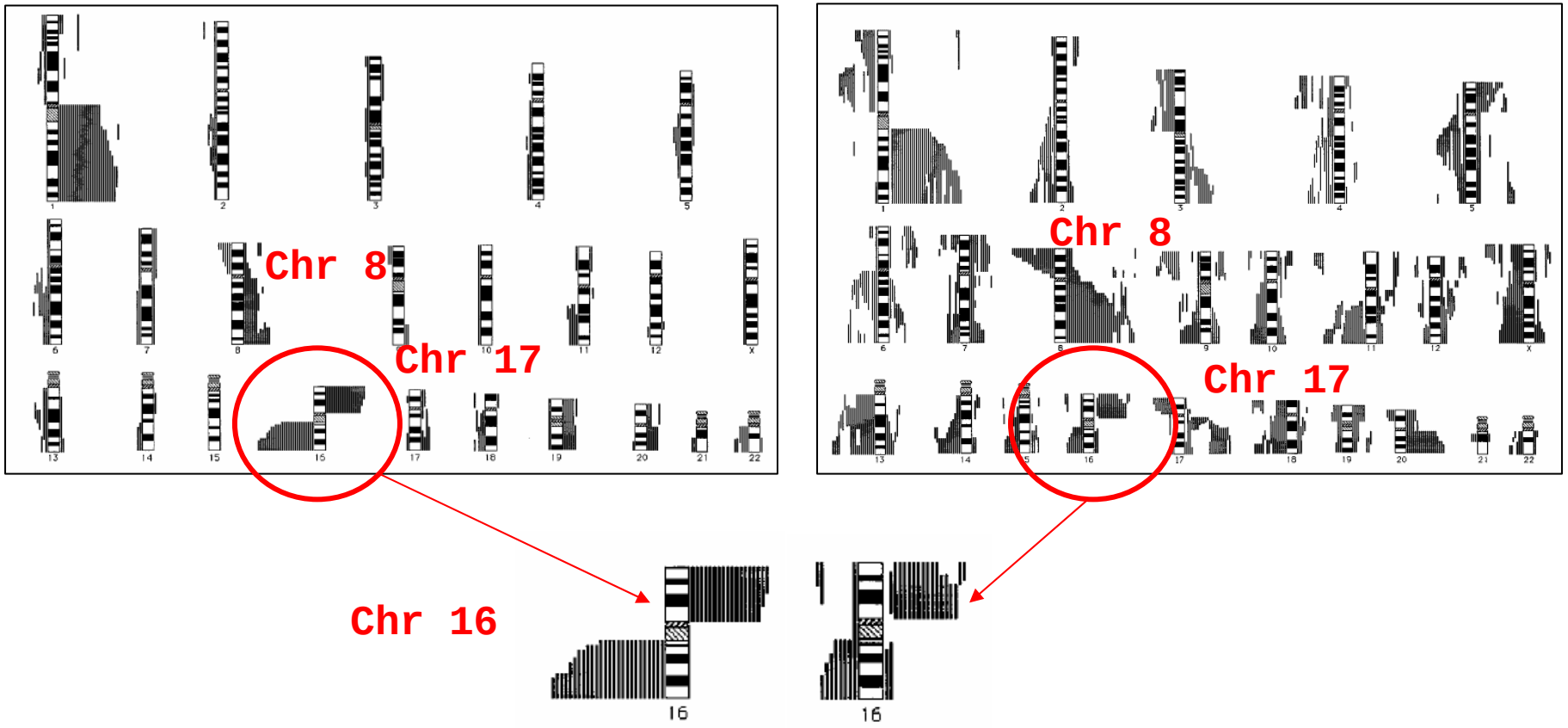
DCIS ► ID occurs independently of tumor grade

Warnberg et al, BJC 2001

Histological Grade and Chromosomal Aberrations

Low grade ID carcinoma

High grade ID carcinoma



65% of grade 1 tumors lost the long arm of Chromosome 16 compared with only 16% of grade 3 tumors

Roylance et al, Cancer Research 1999

Histological Grade and Clinical Outcome

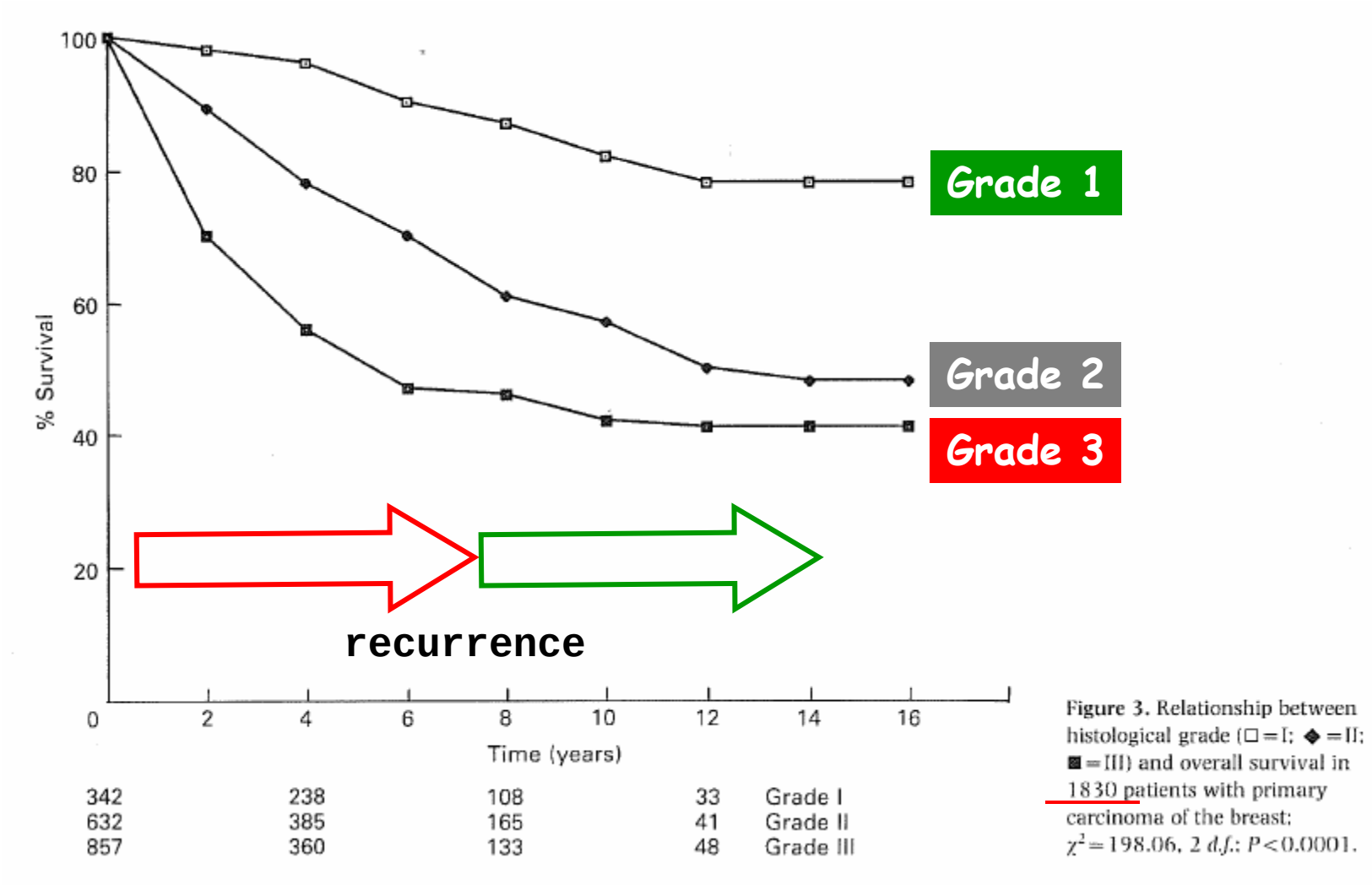
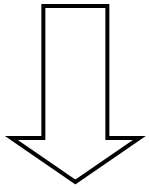


Figure 3. Relationship between histological grade (□ = I; ◆ = II; ■ = III) and overall survival in 1830 patients with primary carcinoma of the breast: $\chi^2 = 198.06$, 2 *d.f.*; $P < 0.0001$.

Elston and Ellis, Histopathology 1991

LOW AND HIGH GRADE TUMORS

TWO DISTINCT DISEASES



Distinct cell type of origin?

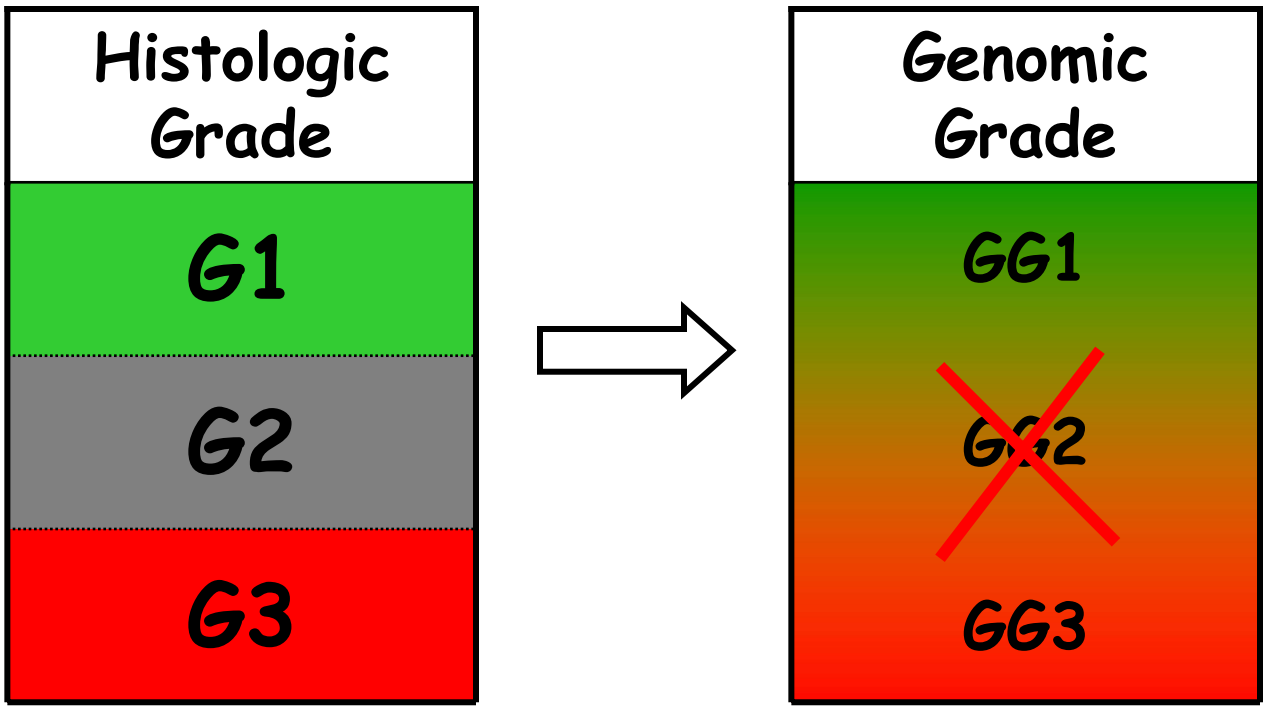
Histological Grade
PROBLEMS

Poor inter observer reproducibility

GRADE 2

Difficult treatment decision making: under- or over- treatment likely

Can we better characterize histological grade?



Gene Expression Profiling in Breast Cancer: Understanding the Molecular Basis of Histologic Grade To Improve Prognosis

Christos Sotiriou, Pratyaksha Wirapati, Sherene Loi, Adrian Harris, Steve Fox, Johanna Smeds, Hans Nordgren, Pierre Farmer, Viviane Praz, Benjamin Haibe-Kains, Christine Desmedt, Denis Larsimont, Fatima Cardoso, Hans Peterse, Dimitry Nuyten, Marc Buyse, Marc J. Van de Vijver, Jonas Bergh, Martine Piccart, Mauro Delorenzi

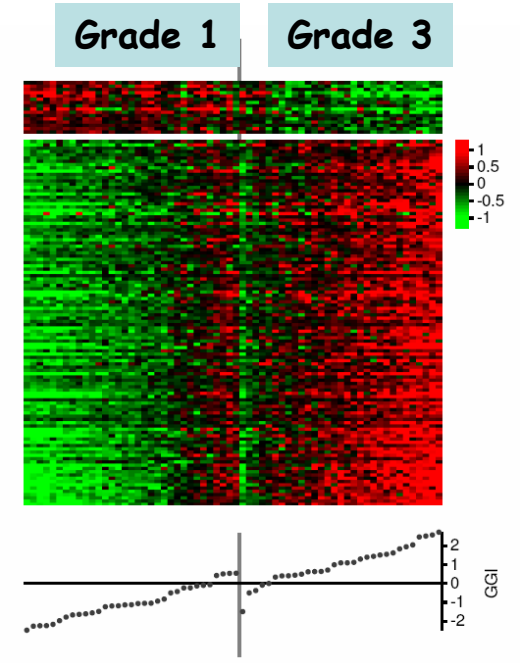
J Natl Cancer Inst. 2006 Feb 15;98(4):262-72

Table 1. Microarray datasets used in this study

Identifier	Institution	No. of samples	Grade ratio* (1/2/3)	% Grade 2	ER ratio* (–/+)	Systemic treatment	Microarray platform	Reference
KJX64	Uppsala	24	11/0/13	0	0/24	Yes†	Affymetrix U133A	Training set (this study)
	John Radcliffe	40	22/0/18	0	0/40			
KJ125	Uppsala	64	26/28/10	44	13/54	No	Affymetrix U133A	Validation set (this study)
	John Radcliffe	61	8/18/18	41	24/32			
NCI	John Radcliffe	99	16/38/45	38	34/65	Yes‡	cDNA (NCI)	Sotiriou et al. *(14)*
STNO	Stanford	85§	9/33/33	44	18/56	Yes‡	cDNA (Stanford)	Sorlie et al. *(12)*
NKI2‖	Nederlands Kanker Instituut	165 (untreated)	40/49/76¶	30	43/122	No	Agilent	Van de Vijver et al. *(15)*
		130 (treated)	35/52/43¶	40	26/104	Yes#		
Total		668						
No. of patients in validation set**		597	134/218/225	38	158/433			

Developing Genomic Grade in the training set

Identify genes correlated with grade 1 vs grade 3



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

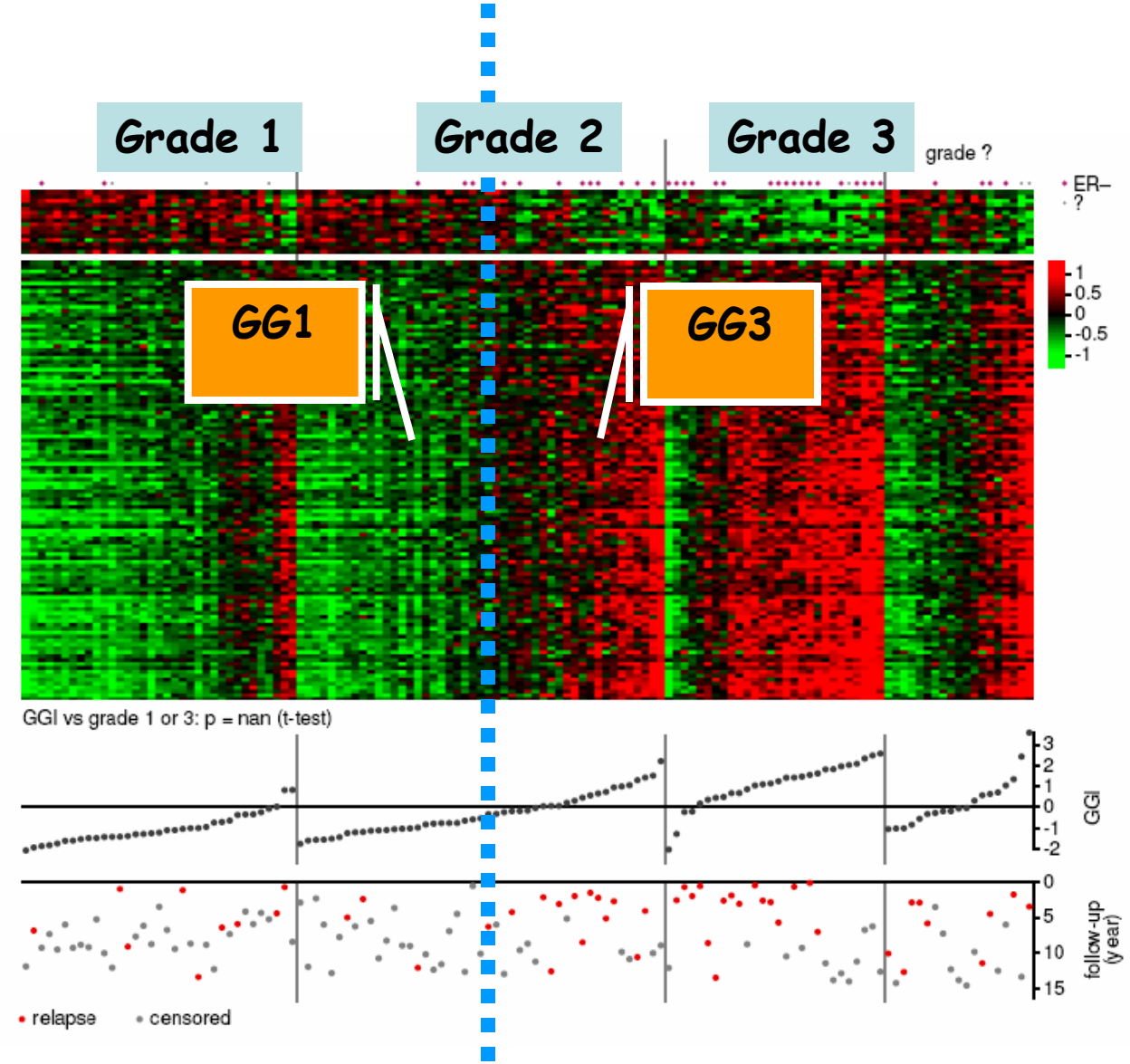
UBE2C RACGAP1 C10orf3 KPNA2
PTTG1 KIF4A TPX2 FOXM1 KIF20A
STK6 STK6 DLG7 DDX39 MELK CCNA2
MYBL2 KIAA0186 BIRC5 NUDT1 KPNA2
KIF2C KIFC1 SPAG5 ASPM CDC20 FEN1
TIMELESS ESPL1 CENPA MCM2
DONSON CDC2 CCNB1 CDCA8 KIF11
DKFZp762E1312 MCM10 CDKN3 MARS
CENPA CCNB2 TRIP13 LMNB1 CDC2
TROAP AURKB FLJ20641 BUB1B
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 …

Define GGI score (gene-expression grade index):

$$\mathrm{GGI} = scale\left(\sum_{j\in G_3} x_j - \sum_{j\in G_1} x_j - offset\right)$$

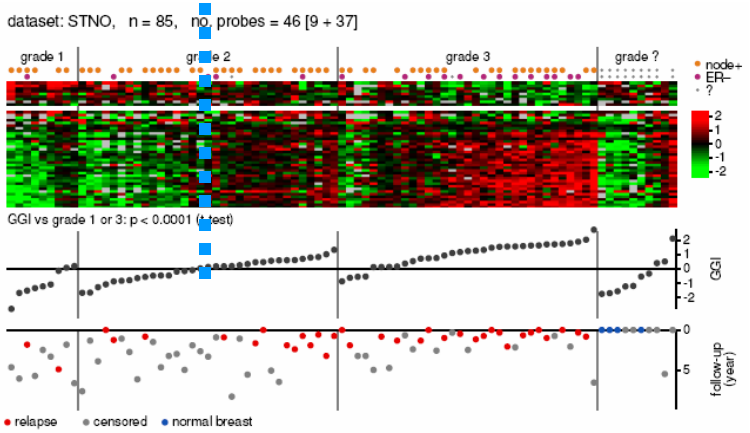
- **Concordance with histological grade**
- **Prognostic value of GGI**

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

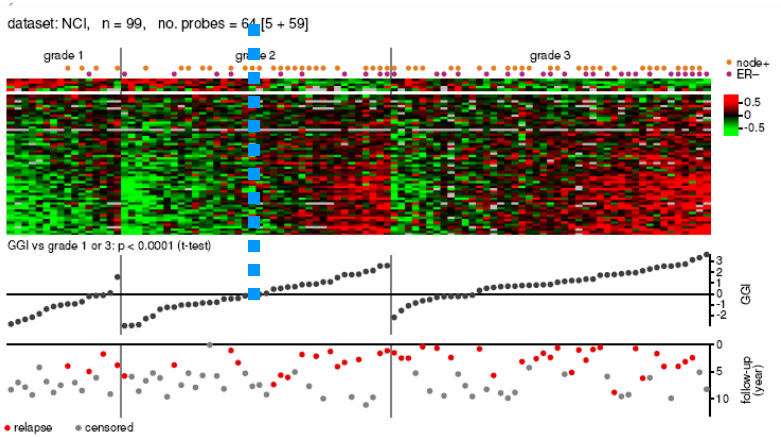


Consistent Distribution of GG in Different Populations and Microarray Platforms

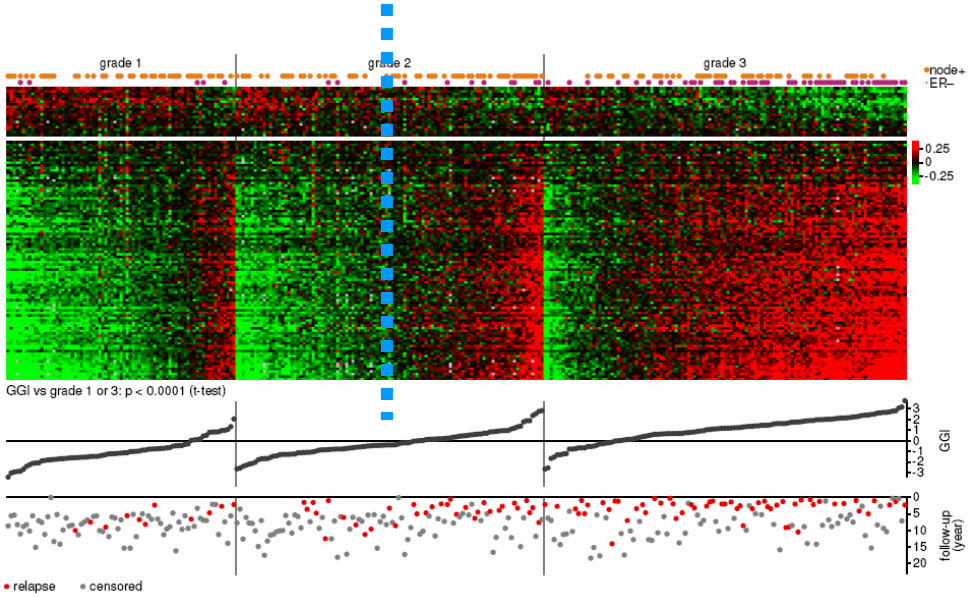
Sorlie et *al.* PNAS 2001



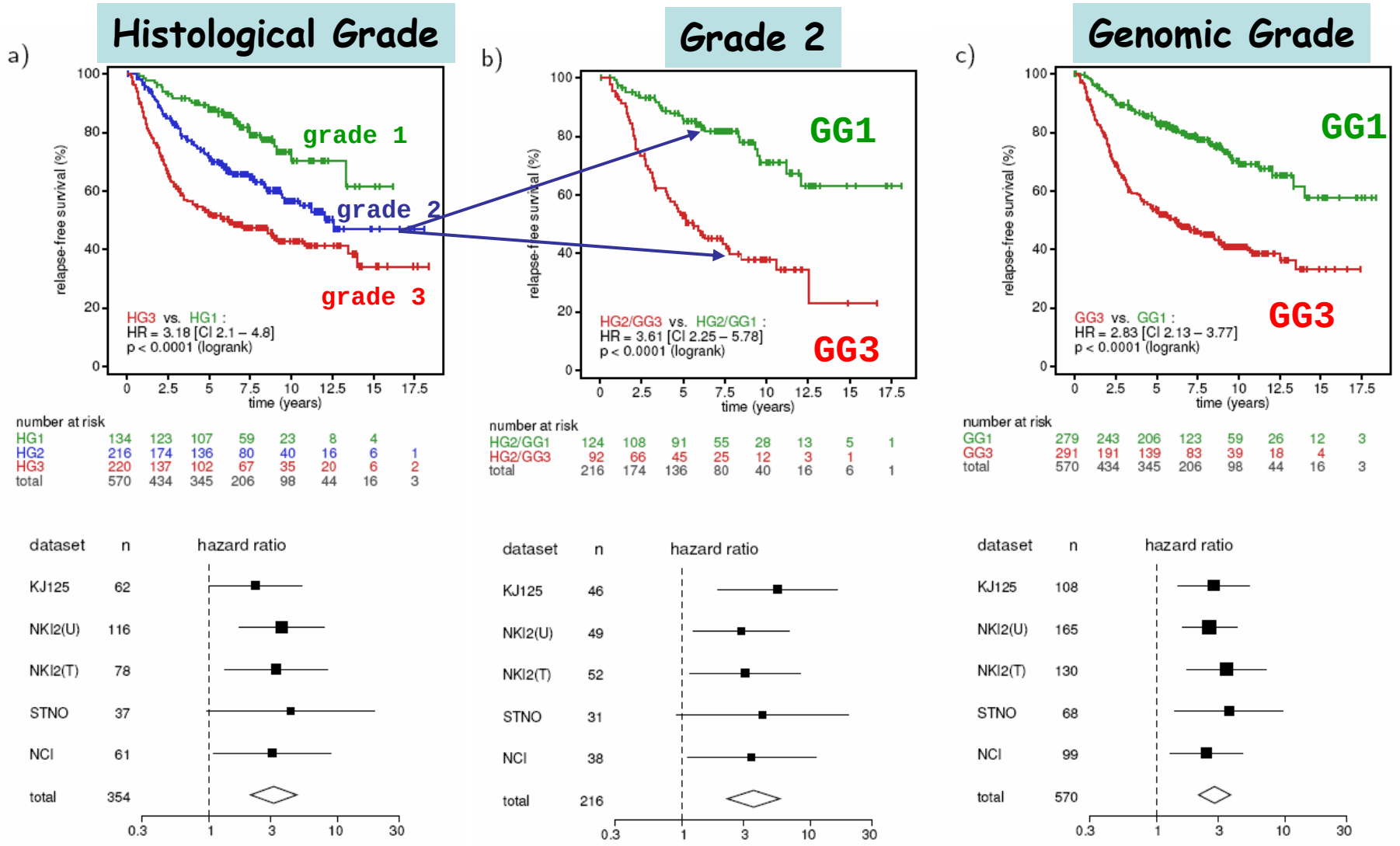
Sotiriou et *al.* PNAS 2003



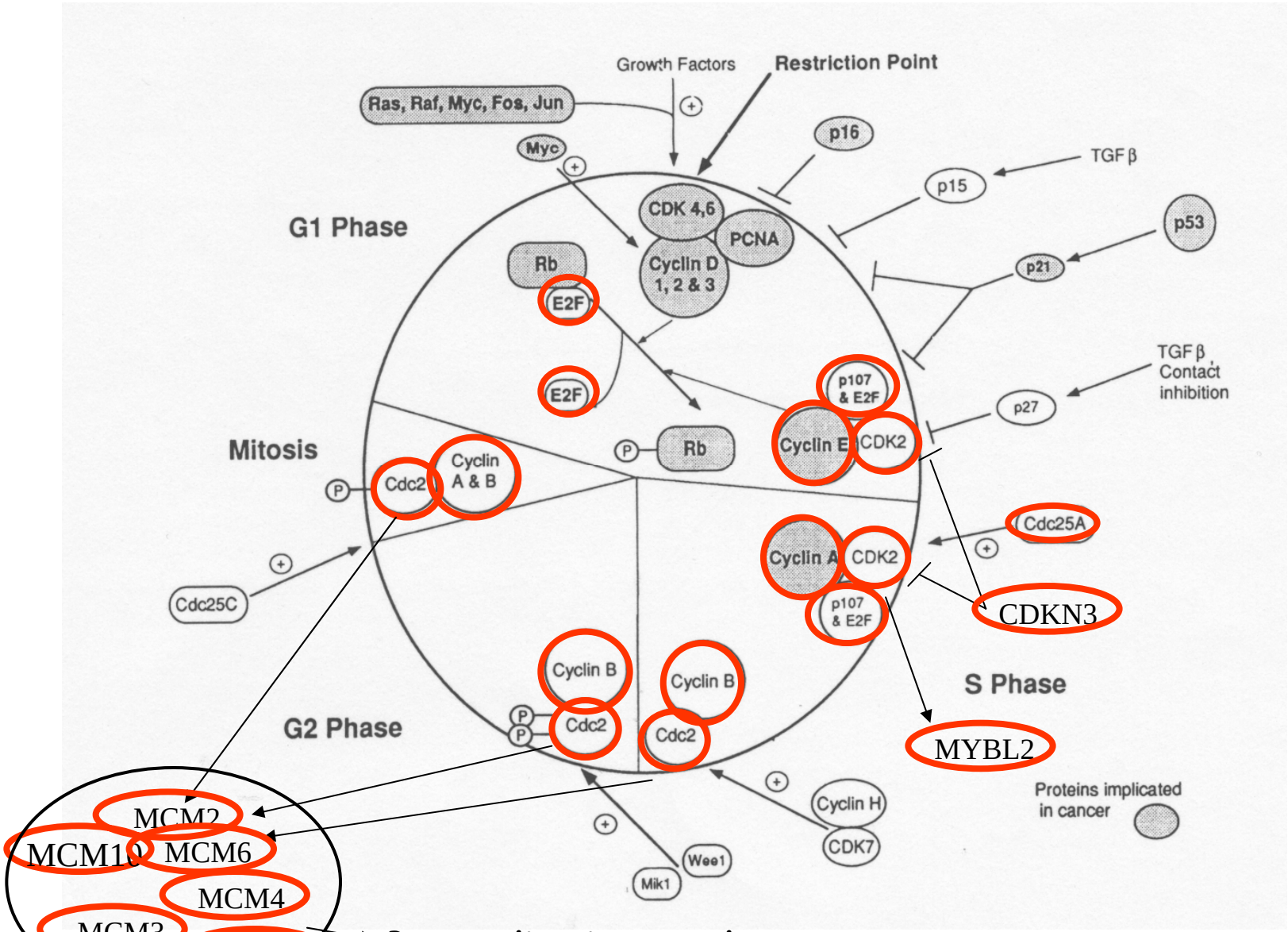
Van de Vijver et *al.* NEJM 2002
Central Pathology Review!



GG and Clinical Outcome



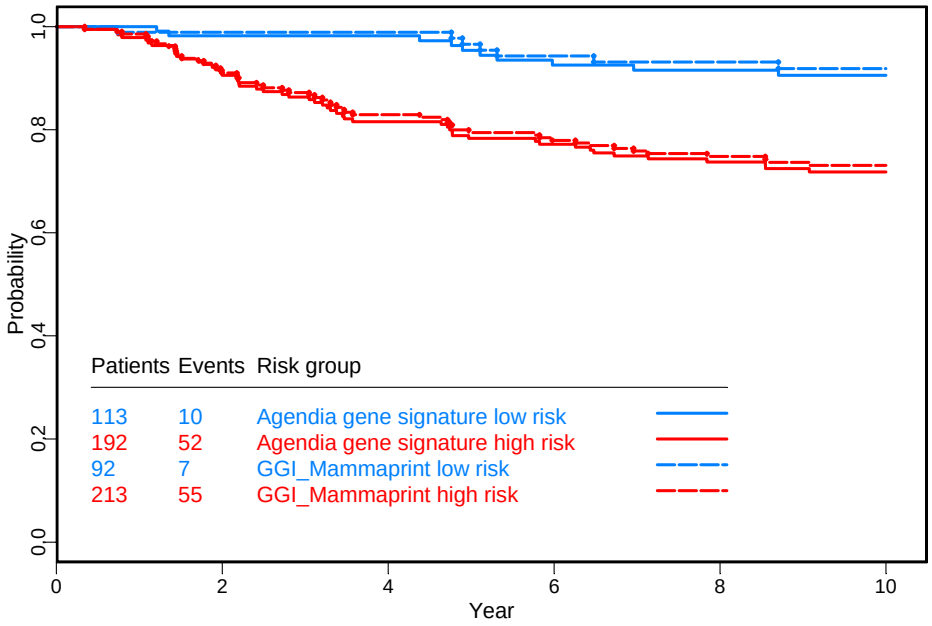
Genomic Grade genes



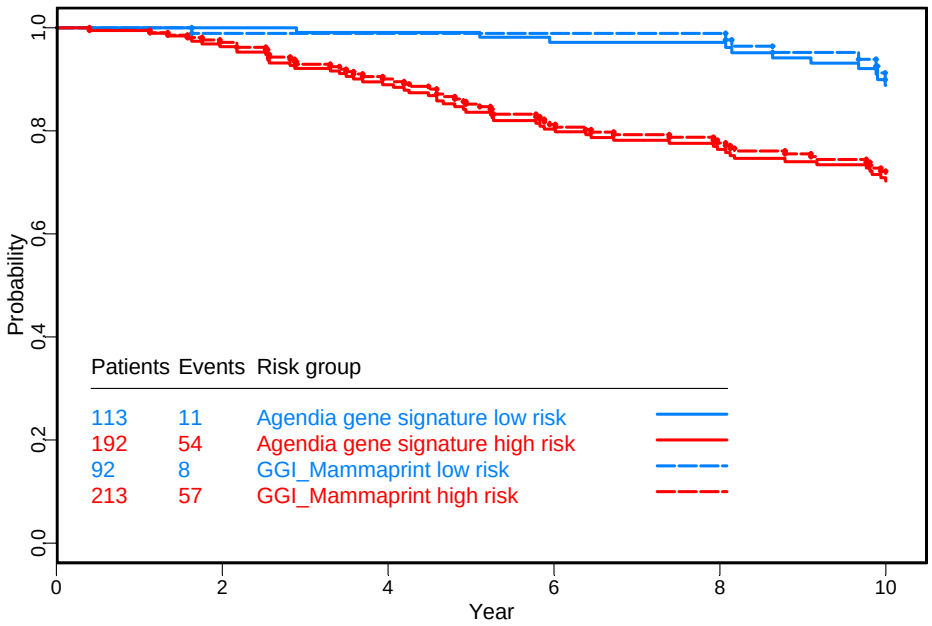
How important are proliferation genes in prognostic gene signatures?

TRANSBIG VALIDATION SERIES
Using MammaPrint® (AGENDIA)
70-genes (AMSTERDAM) versus Genomic Grade

TDM



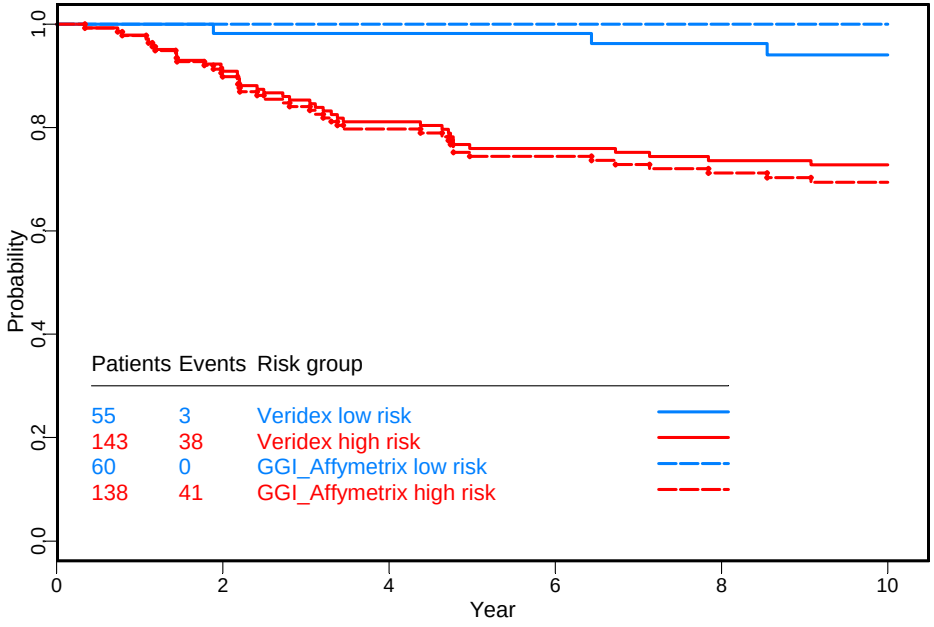
Overall Survival



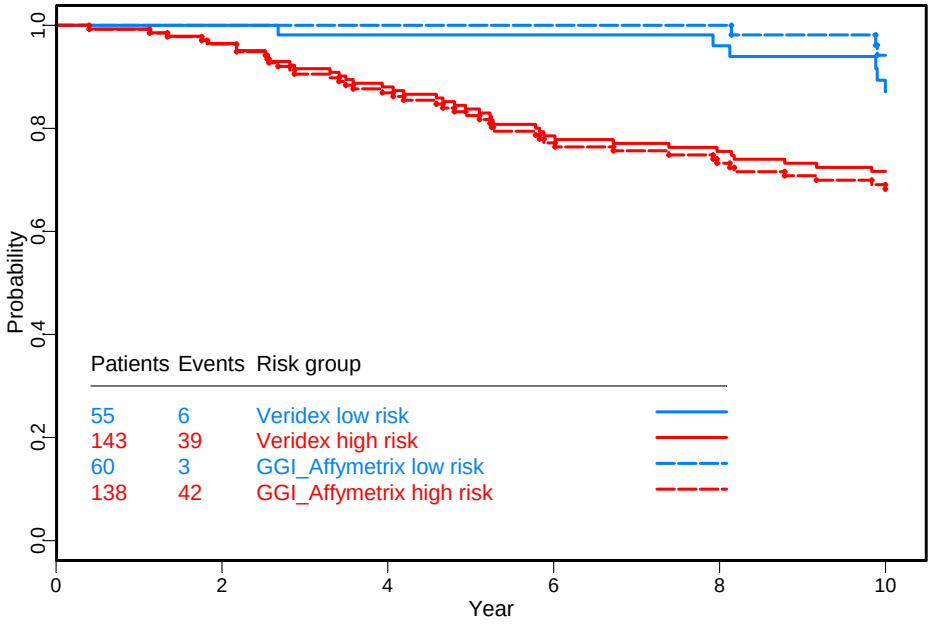
Almost Identical!

TRANSBIG VALIDATION SERIES
Using Affymetrix® (VERIDEX)
76-genes (ROTTERDAM) versus Genomic Grade

TDM



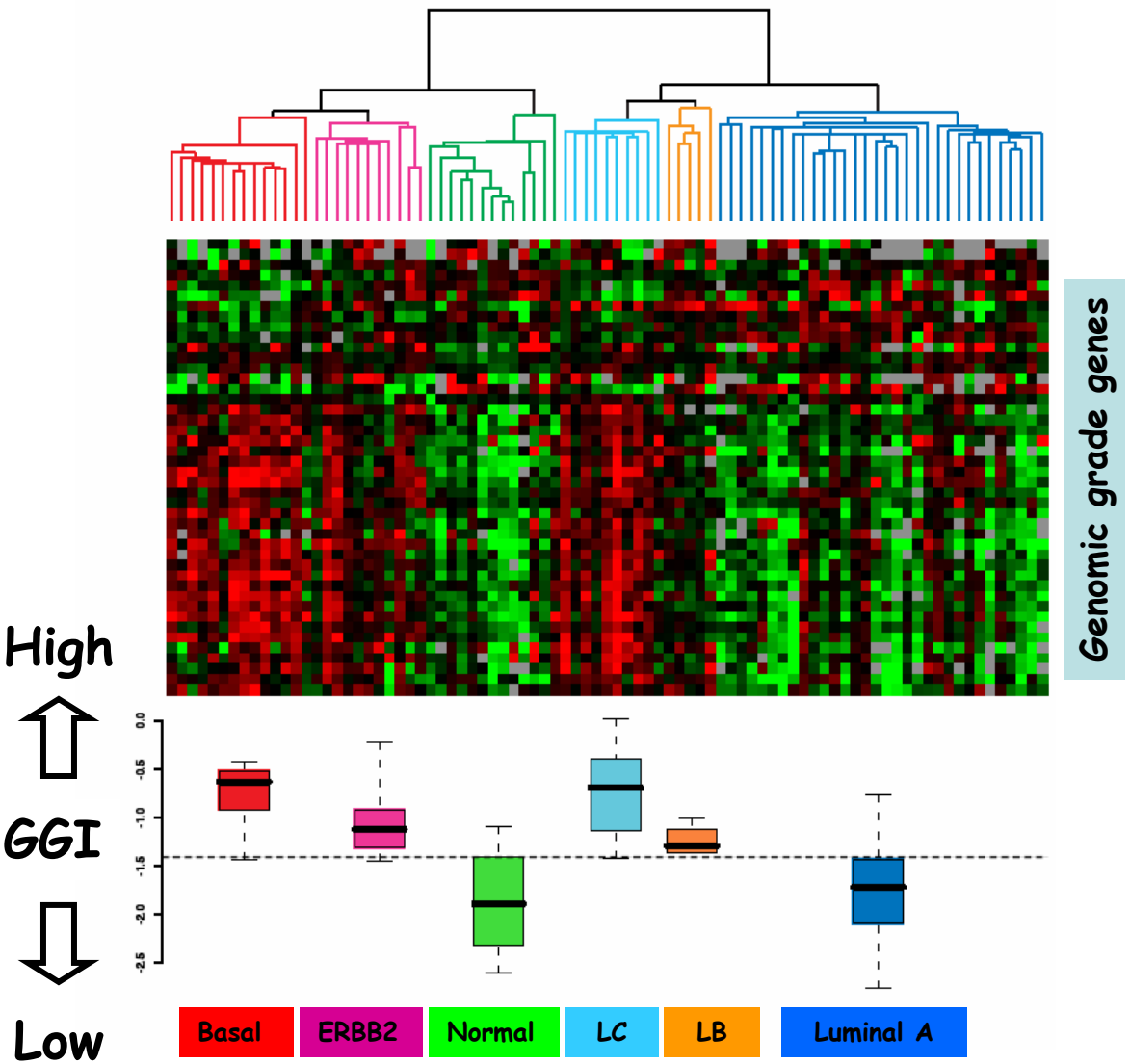
Overall Survival



Almost Identical!

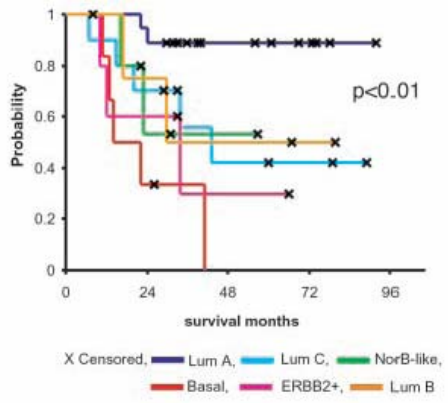
Genomic Grade and Molecular Subtypes

Sotiriou et al. SABCS 2005

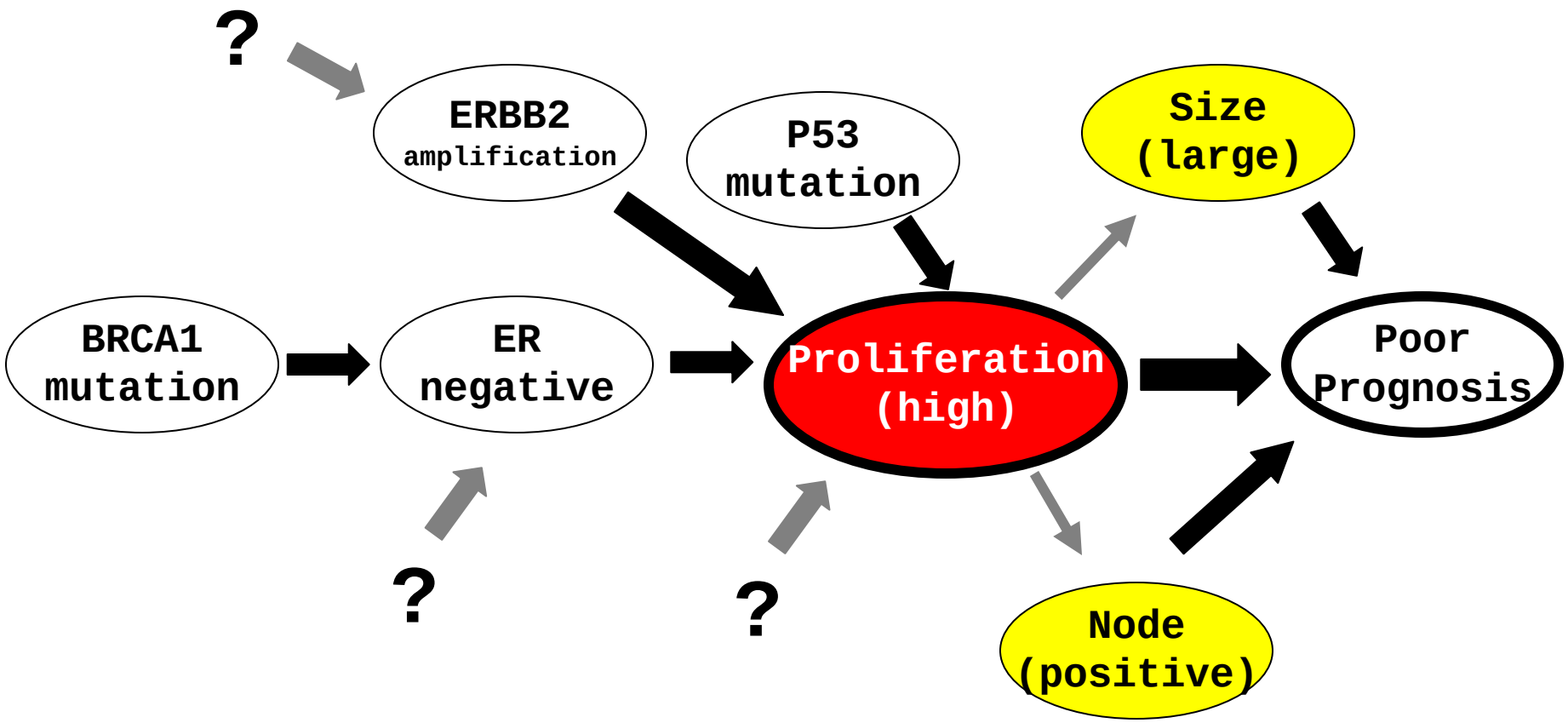


Sorlie *et al.* PNAS 2001

Clinical Outcome

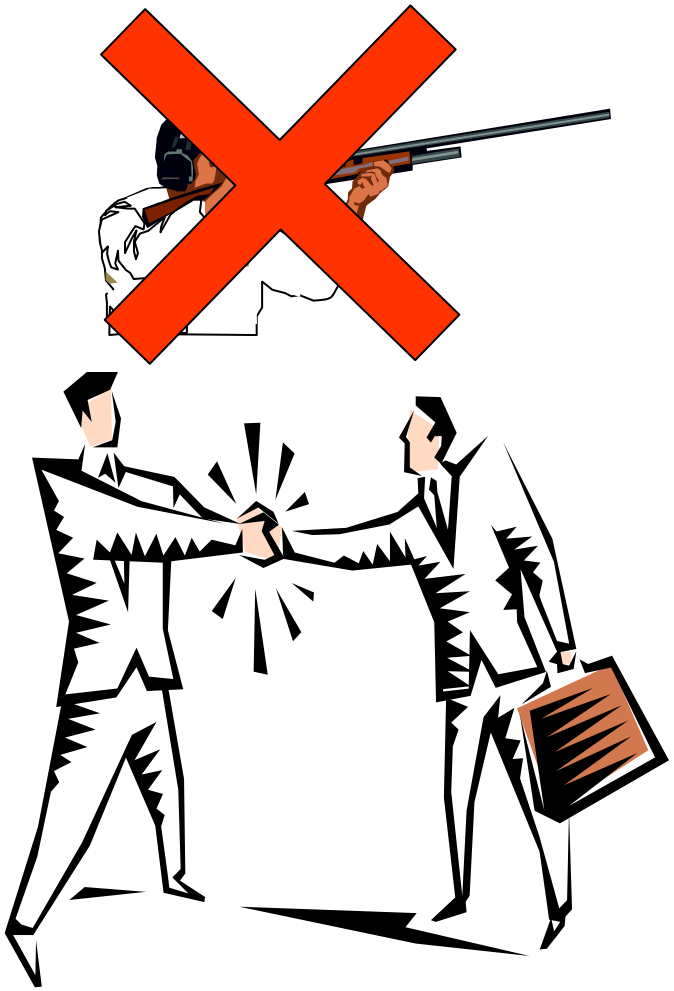


Hypothesis


?
ERBB2
amplification
P53
mutation
Size
(large)
BRCA1
mutation
ER
negative
Proliferation
(high)
Poor
Prognosis
?
?
Node
(positive)

Is genomic grading killing histological grading?

Biologist



Pathologist

Acknowledgements

Prof M. Piccart

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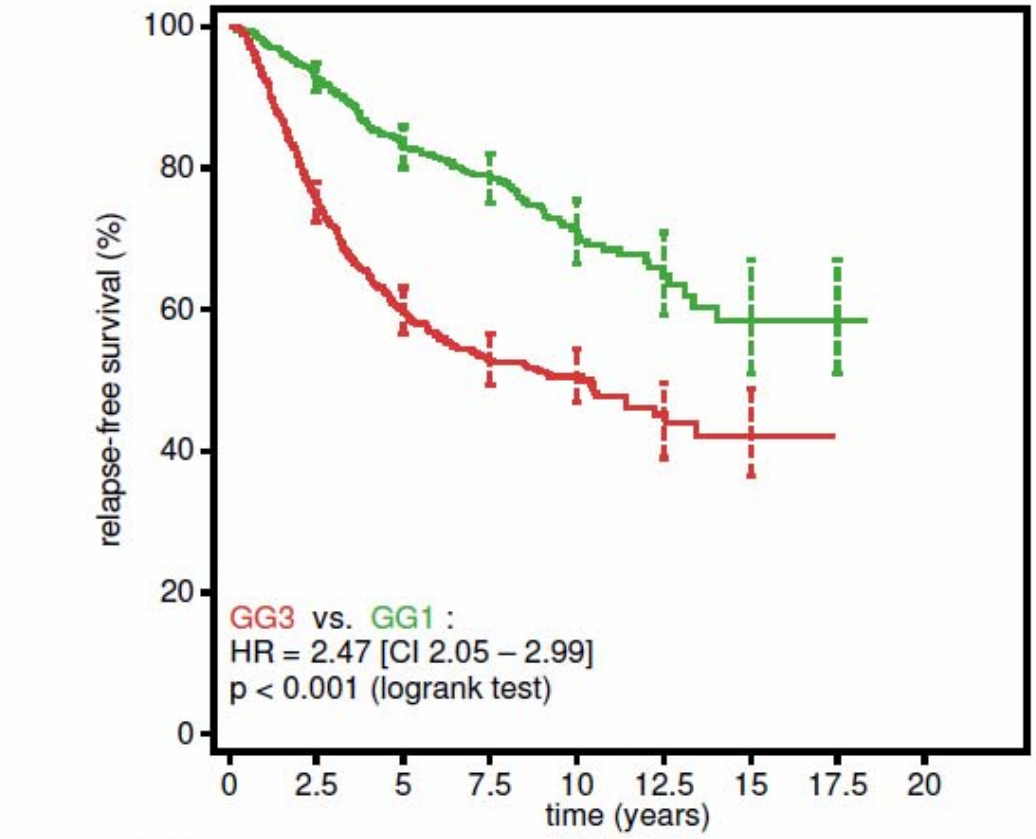
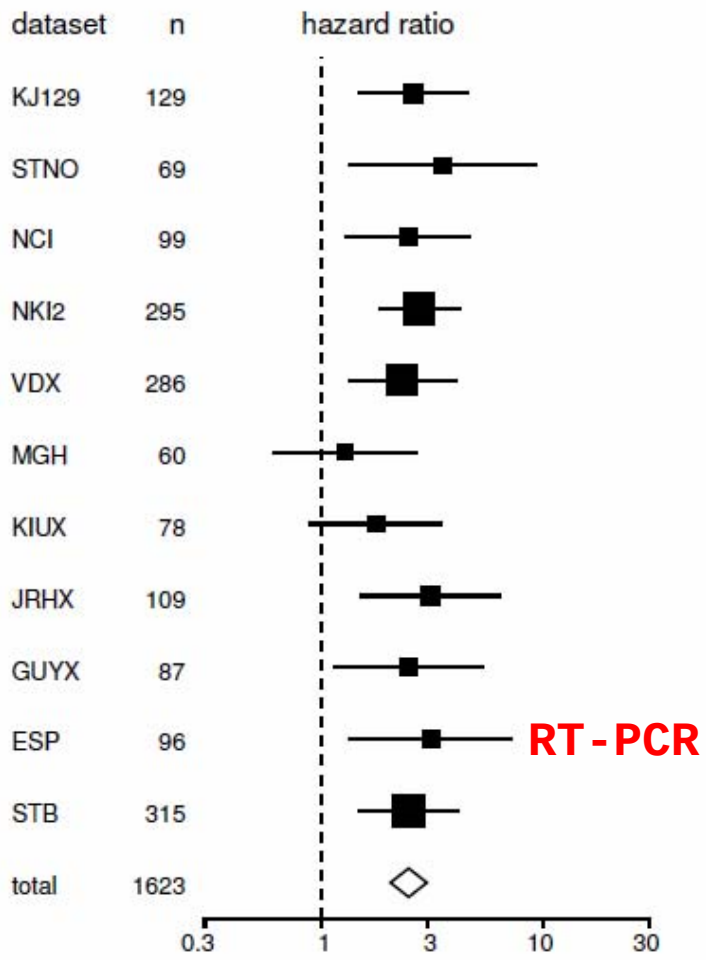
Jonas Bergh
Adrian Harris
Marc Van de Vijver

Backup

META ANALYSIS
11 studies
1623 patients





The relationship between ER, grade and prognosis

a)

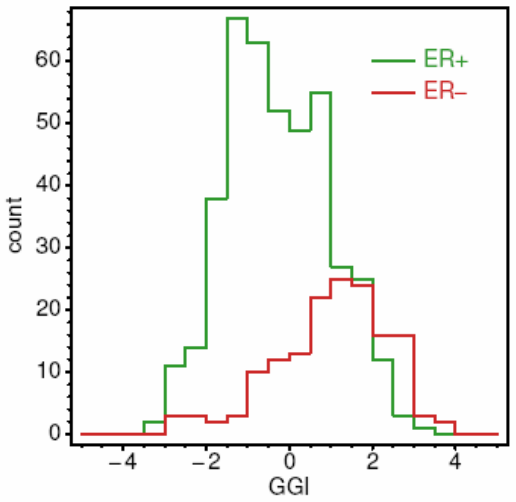
counts

	HG1	HG2	HG3	total
ER–	8	38	107	153
ER+	123	179	116	418
total	131	217	223	571

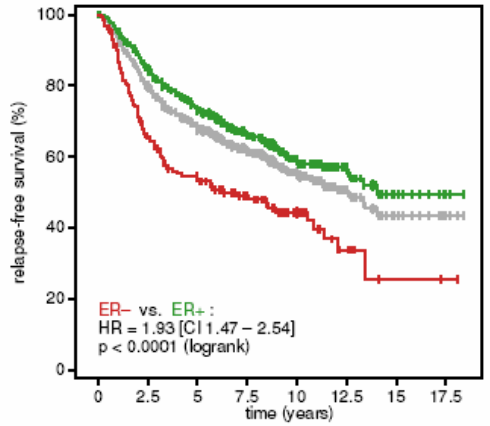
percentage

	HG1	HG2	HG3	total
ER–	1.4	6.7	18.7	26.8
ER+	21.5	31.3	20.3	73.2
total	22.9	38.0	39.1	100.0

b)



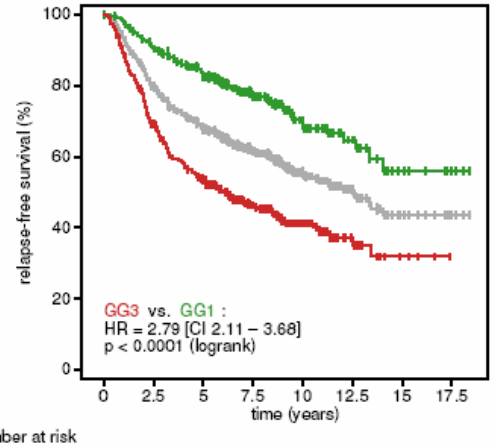
c)



number at risk

ER+	427	349	280	162	81	38	14	2
ER–	153	95	72	49	23	9	2	1
total	580	444	352	211	104	47	16	3

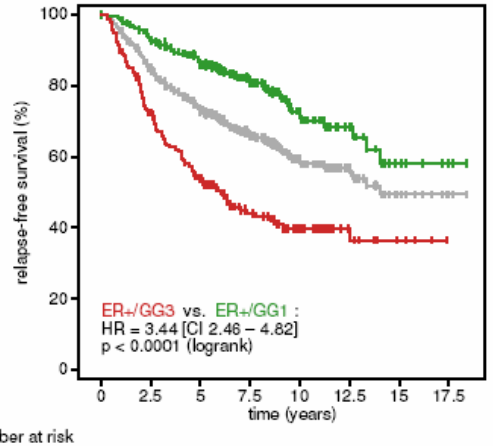
d)



number at risk

GG1	287	251	211	127	64	30	12	3
GG3	293	193	141	84	40	17	4	
total	580	444	352	211	104	47	16	3

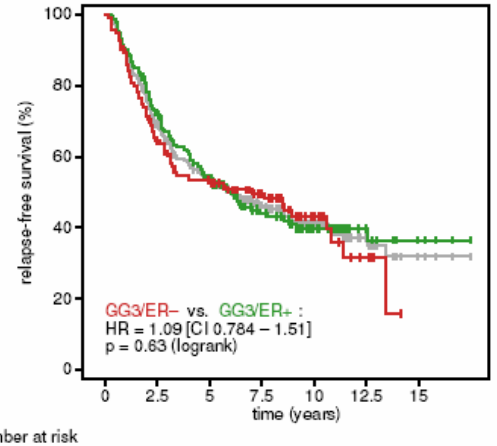
e)



number at risk

ER+/GG1	255	229	195	116	56	26	10	2
ER+/GG3	172	120	85	46	25	12	4	
total	427	349	280	162	81	38	14	2

f)

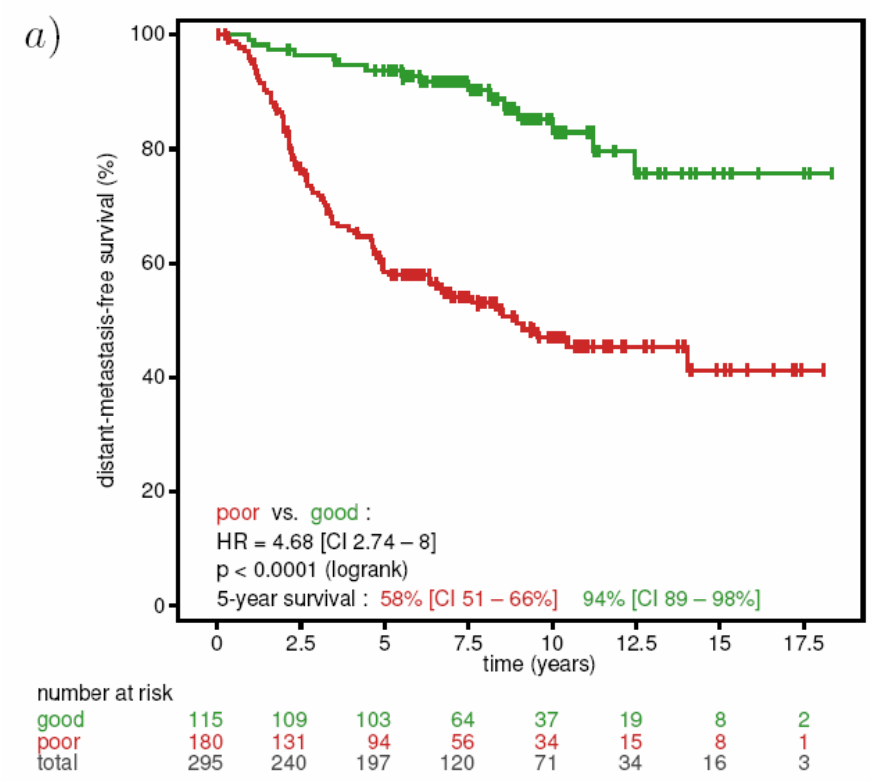


number at risk

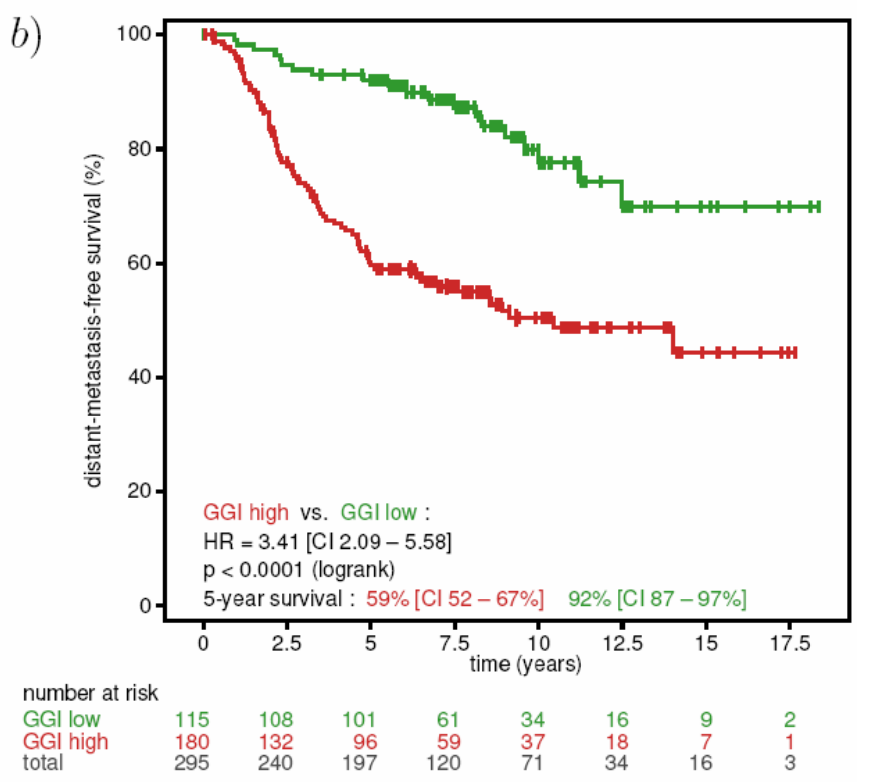
GG3/ER+	172	120	85	46	25	12	4
GG3/ER–	121	73	56	38	15	5	
total	293	193	141	84	40	17	4

Relationship with the 70-gene Amsterdam Signature

70-genes



Genomic Grade



Based on 113 probe (93 genes) mapped on the Agilent arrays