Gene expression profiles; a comprehensive overview

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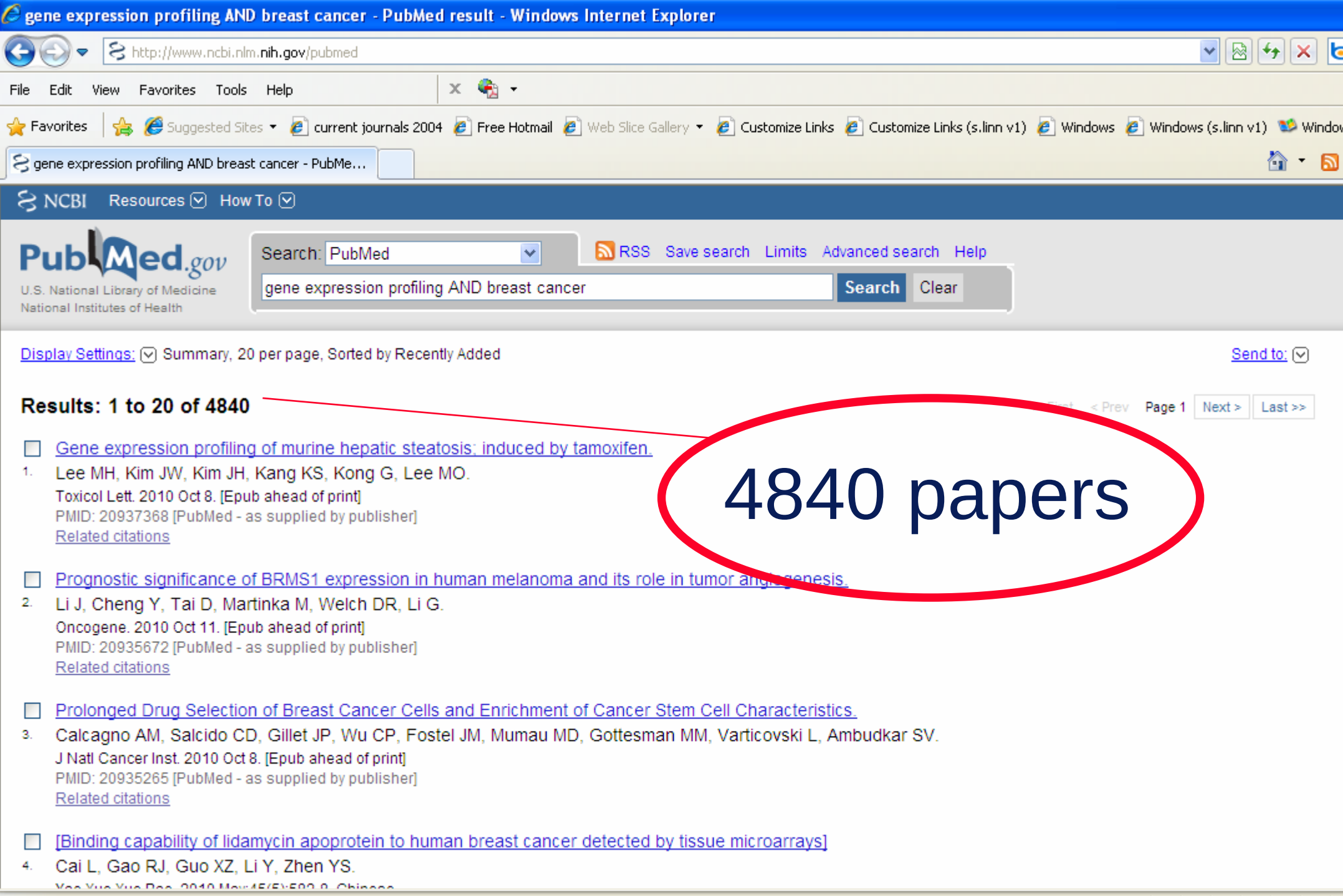
Amsterdam


gene expression profiling AND breast cancer - PubMed result - Windows Internet Explorer
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NCBI Resources How To
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National Institutes of Health
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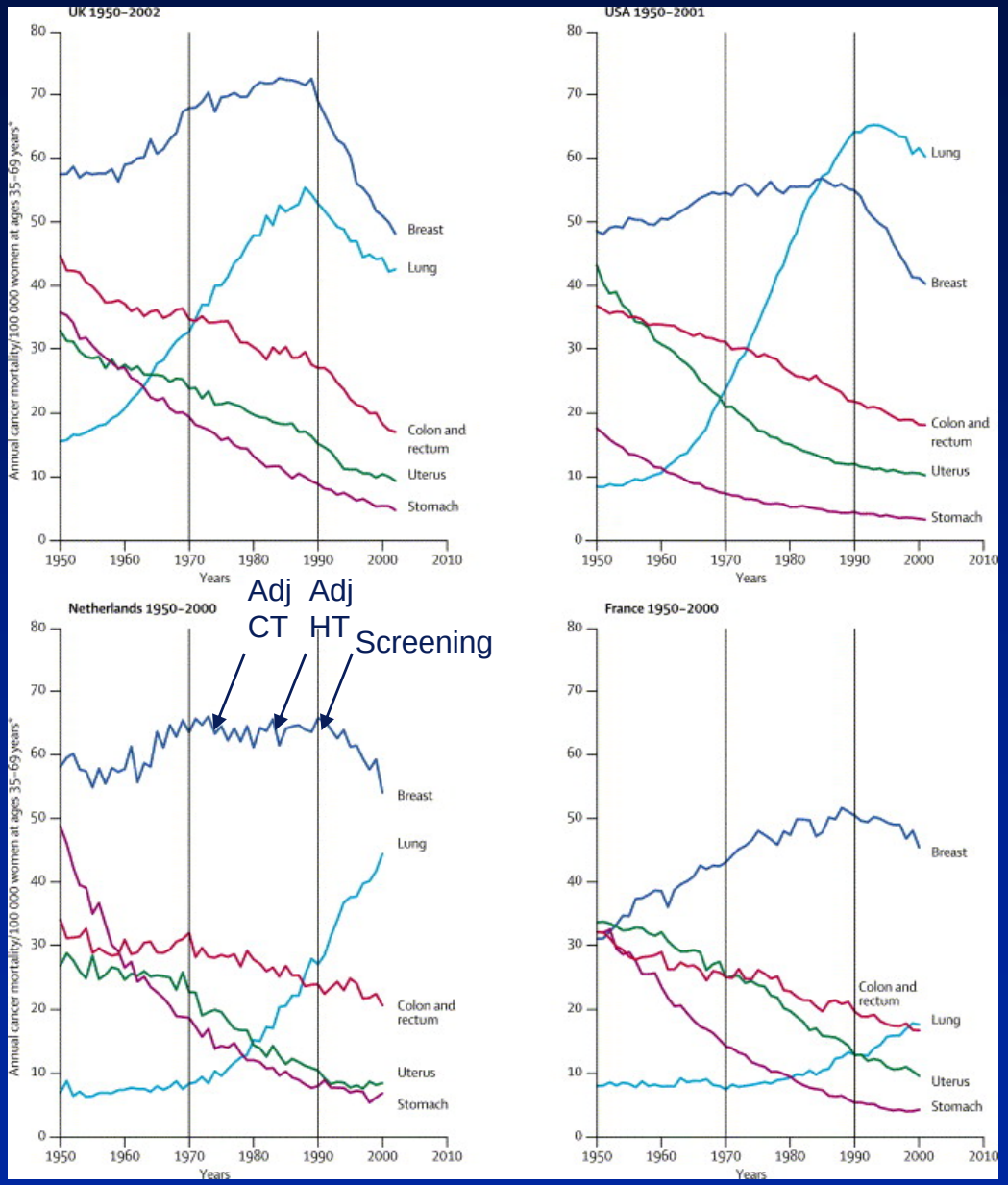
gene expression profiling AND breast cancer
Search Clear
Display Settings: Summary, 20 per page, Sorted by Recently Added
Send to:
Results: 1 to 20 of 4840
< Prev Page 1 Next > Last >>
Gene expression profiling of murine hepatic steatosis: induced by tamoxifen.
1. Lee MH, Kim JW, Kim JH, Kang KS, Kong G, Lee MO.
Toxicol Lett. 2010 Oct 8. [Epub ahead of print]
PMID: 20937368 [PubMed - as supplied by publisher]
Related citations
Prognostic significance of BRMS1 expression in human melanoma and its role in tumor angiogenesis.
2. Li J, Cheng Y, Tai D, Martinka M, Welch DR, Li G.
Oncogene. 2010 Oct 11. [Epub ahead of print]
PMID: 20935672 [PubMed - as supplied by publisher]
Related citations
Prolonged Drug Selection of Breast Cancer Cells and Enrichment of Cancer Stem Cell Characteristics.
3. Calcagno AM, Salcido CD, Gillet JP, Wu CP, Fostel JM, Mumau MD, Gottesman MM, Varticovski L, Ambudkar SV.
J Natl Cancer Inst. 2010 Oct 8. [Epub ahead of print]
PMID: 20935265 [PubMed - as supplied by publisher]
Related citations
[Binding capability of lidamycin apoprotein to human breast cancer detected by tissue microarrays]
4. Cai L, Gao RJ, Guo XZ, Li Y, Zhen YS.
4840 papers

Recent decline in breast cancer mortality in the UK, USA, NL, FR: 35-69 years



Interpretation of Peto et al. Lancet, 2005

Taxane vs no chemo

(i) age <50

	RECURRENCE rate ratio (se), years 0-4 only	BREAST CANCER MORTALITY rate ratio (se)
CMF vs no chem	0.56 (0.05)	0.68 (0.05)
Anthr. vs CMF	0.84 (0.05)	0.81 (0.05)
Taxane vs Anthr.	0.84 (0.04)	0.86 (0.05)
Taxane vs no chem (multiplying 3 RRs)	0.38 (0.07) 2p<0.00001	0.46 (0.08) 2p<0.00001

SABCS 2007

Courtesy Richard Peto

Taxane vs no chemo

(ii) age 50-69

	RECURRENCE rate ratio (se), years 0-4 only	BREAST CANCER MORTALITY rate ratio (se)
CMF vs no chem	0.75 (0.03)	0.91 (0.03)
Anthr. vs CMF	0.89 (0.06)	0.90 (0.06)
Taxane vs Anthr	0.82 (0.04)	0.84 (0.05)
Taxane vs no chem (multiplying 3 RRs)	0.52 (0.07) 2p<0.00001	0.66 (0.08) 2p=0.00002

SABCS 2007

Courtesy Richard Peto

Why do we need prognostic markers?

- Should all patients receive all adjuvant therapy?
  - Depends on:
    - Prognostic and Predictive Factors
    - Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy
      - No patient with invasive breast cancer has a zero chance of recurrence and death
      - No patient has a zero chance of benefit from any therapy
- If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything*
- If pt is willing to forego SOME benefit to avoid SOME toxicity: *then select therapy carefully*

Courtesy Daniel Hayes

Benefit adjuvant chemotherapy

Rule of thumb:

Chemotherapy: relative risk reduction 10 yrs † risk: 30 – 50%

♦ Absolute benefit	< 50 yrs	N0:	10 %
		N+:	25 %
	50-69 yrs	N0:	5 %
		N+:	10 %

But: > 50 yrs and hormone receptor negative: same as < 50 jr

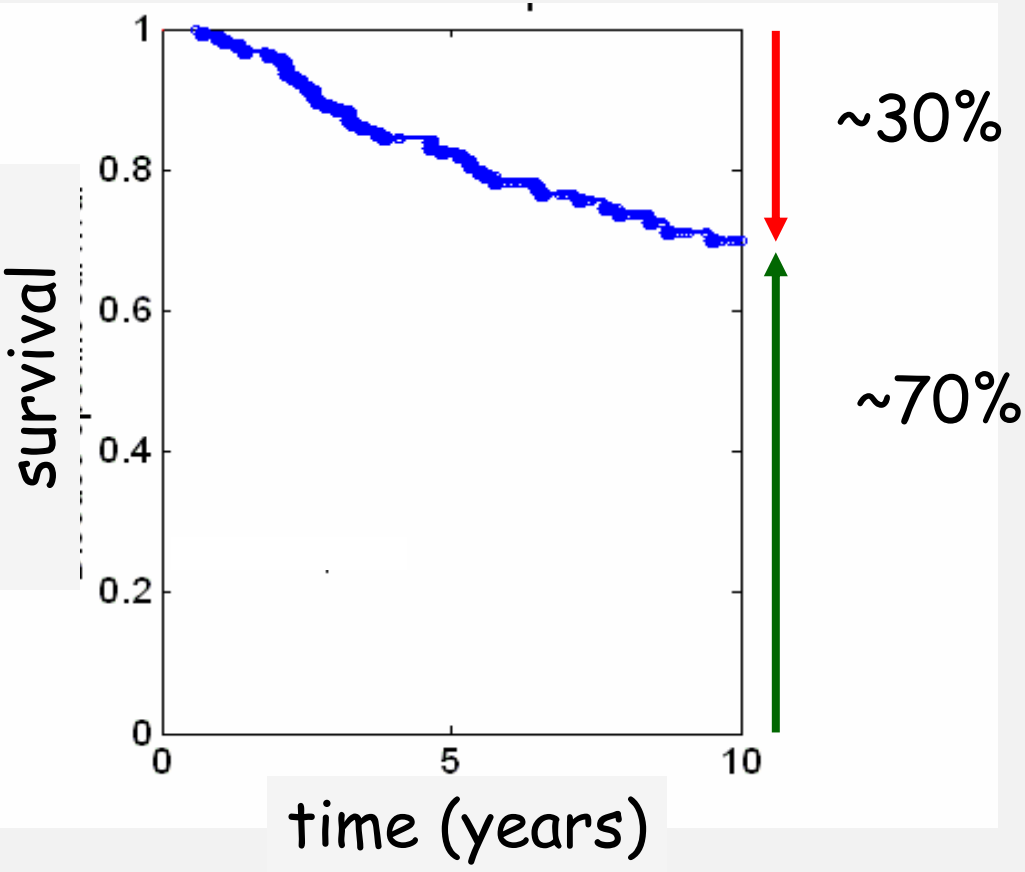
Factors that influence the advice

- Age
- Lymph node status
- Tumor size
- Differentiation grade
- Histological subtype
- Co-morbidity
- Oestrogen / progesterone receptor status
- HER2/neu receptor status

Breast Cancer - Survival

premenopausal patients, lymph node negative

Kaplan-Meier Survival Curves



~30% die of breast cancer

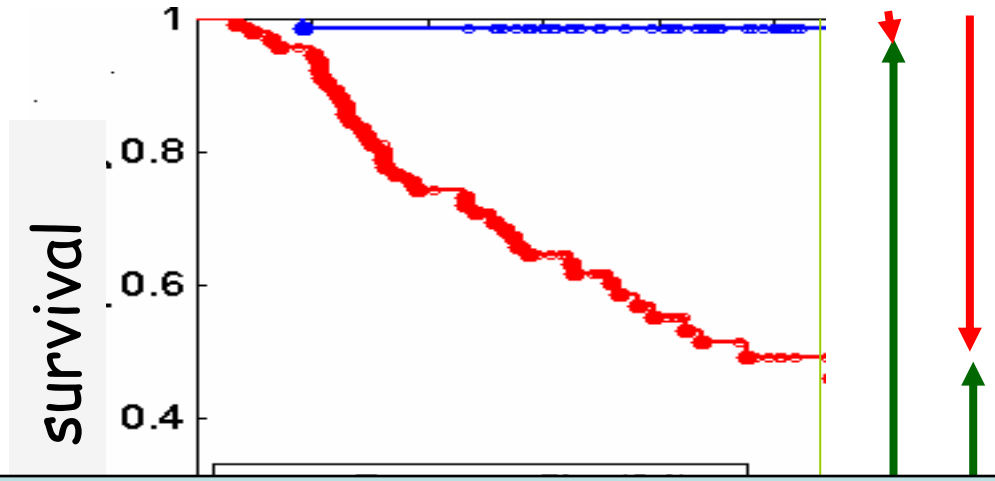
~70% survive breast cancer

1) Who to treat

2) How to treat

Breast cancer survival according to the 70-gene profile

Discerns: 40% favorable profile, 60% unfavorable profile



favorable profile:
~4% dies of breast cancer
~96% survives breast cancer

unfavorable profile:

Data confirmed by 2 independent studies:
Buyse et al. and Bueno-de-Mesquita et al.

Van de Vijver et al. NEJM 2002

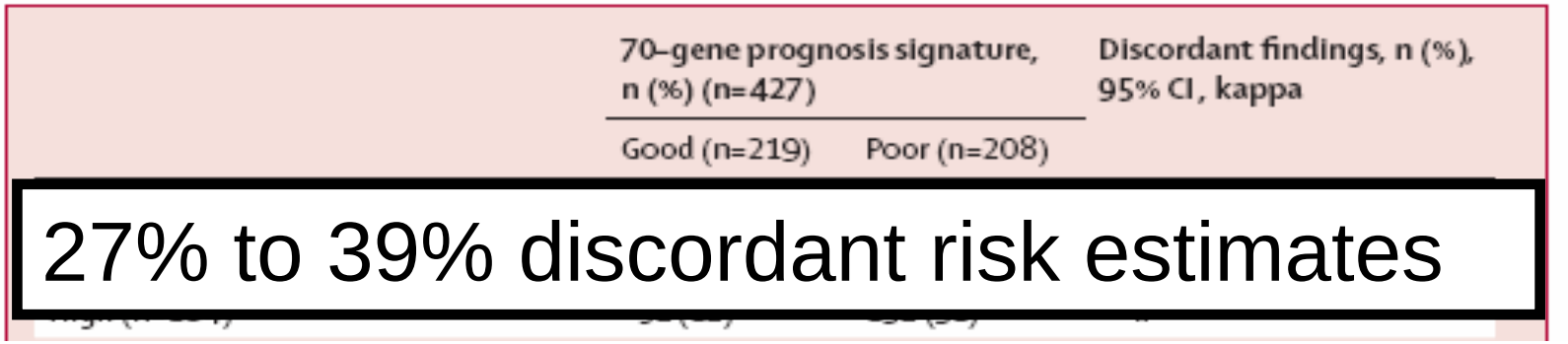
10-years survival data

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

http://oncology.thelancet.com Vol 8 December 2007

Discordant risk estimates MammaPrint vs clinical guidelines



	70-gene prognosis signature, n (%) (n=427)		Discordant findings, n (%), 95% CI, kappa
	Good (n=219)	Poor (n=208)	

27% to 39% discordant risk estimates

~30 % discordant risk estimates resulted in changed therapy advice in ~20% of patients (mammaprint should be combined with clinico-pathological factors)

At least 13 commercial tests

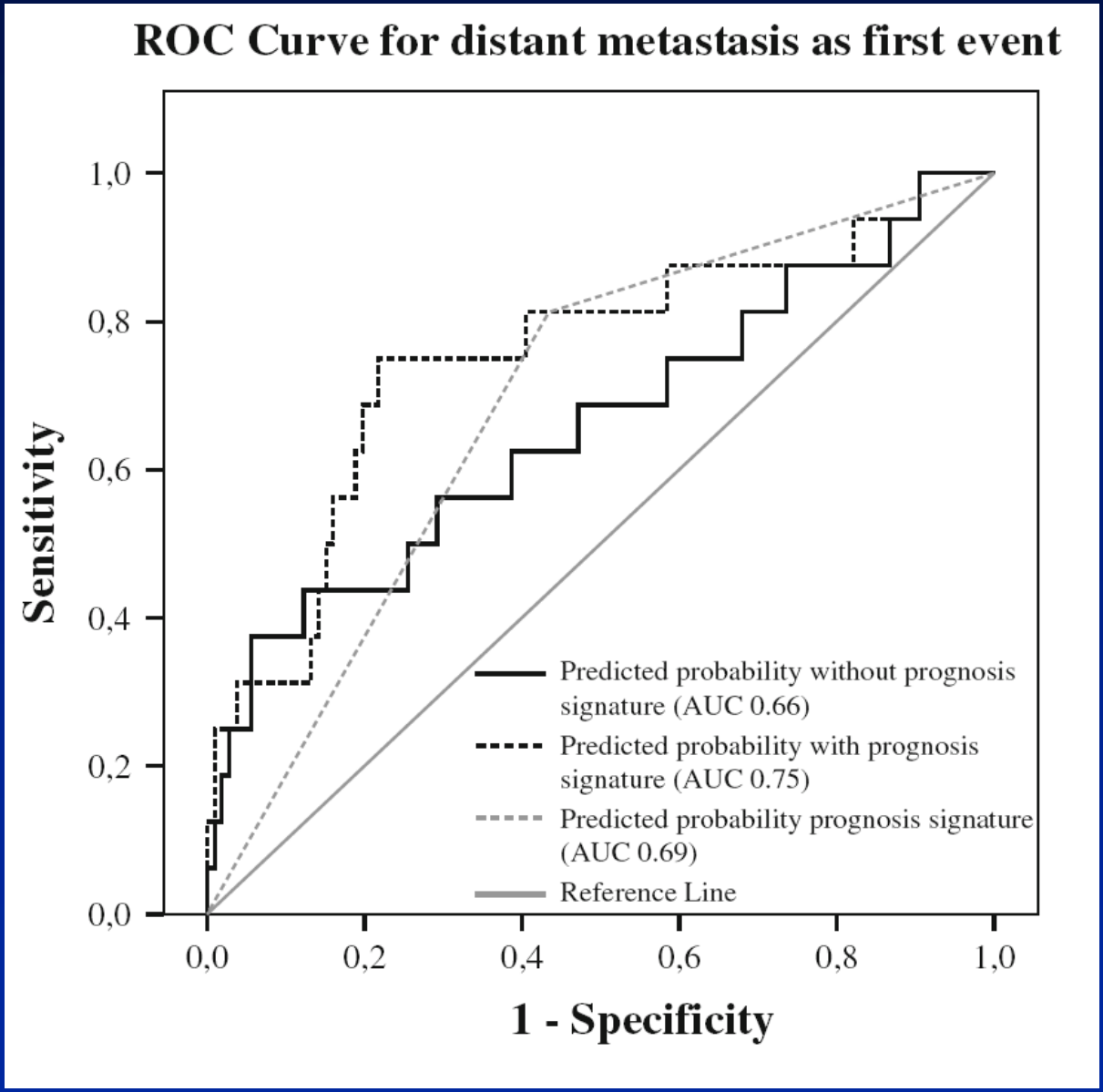
Test	Classification		Grading	Prognosis only
	Sorlie-Perou classifier	ARUP bioclassifier	Sotiriou molecular grading	ProEx™ Br
Prognosis only				
Mammostrat®	eXagen*BC*	MammaPrint®	Invasiveness gene signature	onco*type* DX™
Prognosis and response to therapy				
Two-gene ratio	Celera metastasis score	Rotterdam signature	NuvoSelect™ (TFAC/ER)	Roche AmpliChip® (cytochrome P450 CYP2D6)

Ross, Oncologist 2008

Differences between Mammaprint and Oncotype DX

	Mammaprint	Oncotype DX
For whom?	ER pos N0 Untreated	ER pos N0 TAM-treated
Tissue fixation	Frozen	FFPE
Histology	Ductal	Ductal
Predictive for tamoxifen benefit?	?	Yes
Predictive for chemotherapy benefit?	No	Yes
Prognostic in HER2 pos?	Yes	No

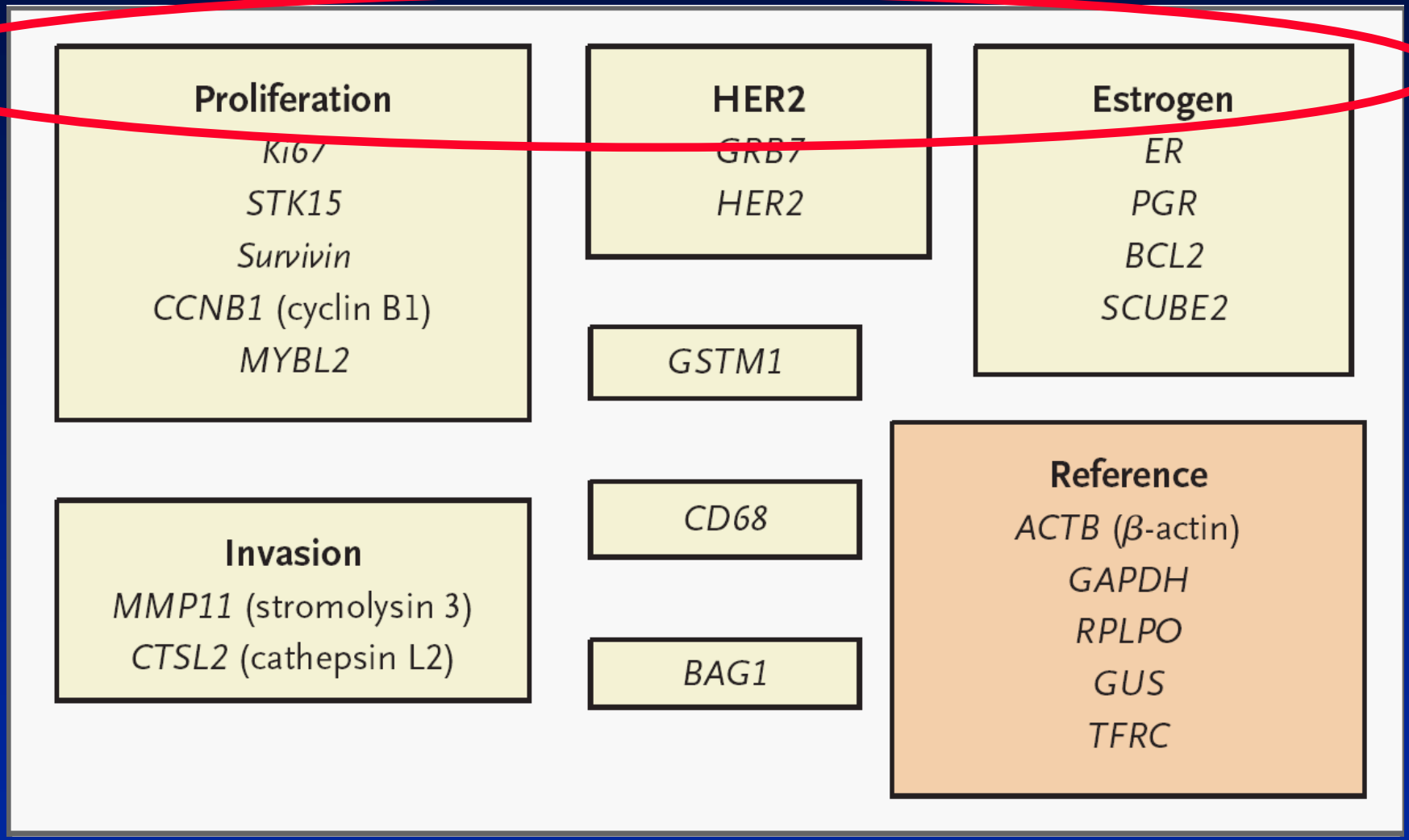
Does Mammaprint add prognostic information?



	AUC
Clinical	0.66
Clinical + MP	0.75
MP only	0.69

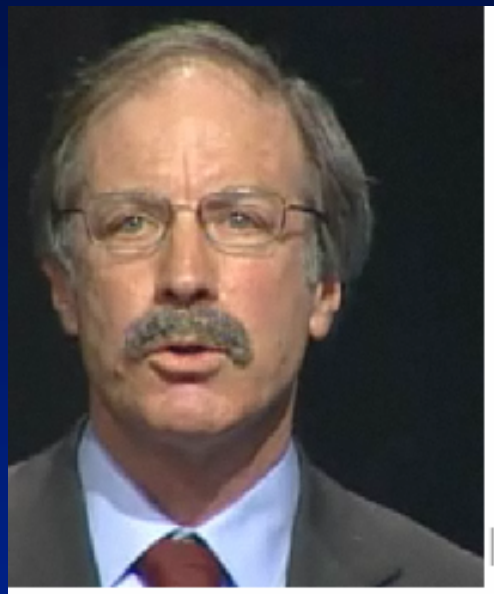
Bueno-de-Mesquita, Breast Cancer Res Treat, 2008

Does Oncotype DX add prognostic information?



IHC4=ER / PR / HER2 /Ki67

Does Oncotype DX add prognostic information?



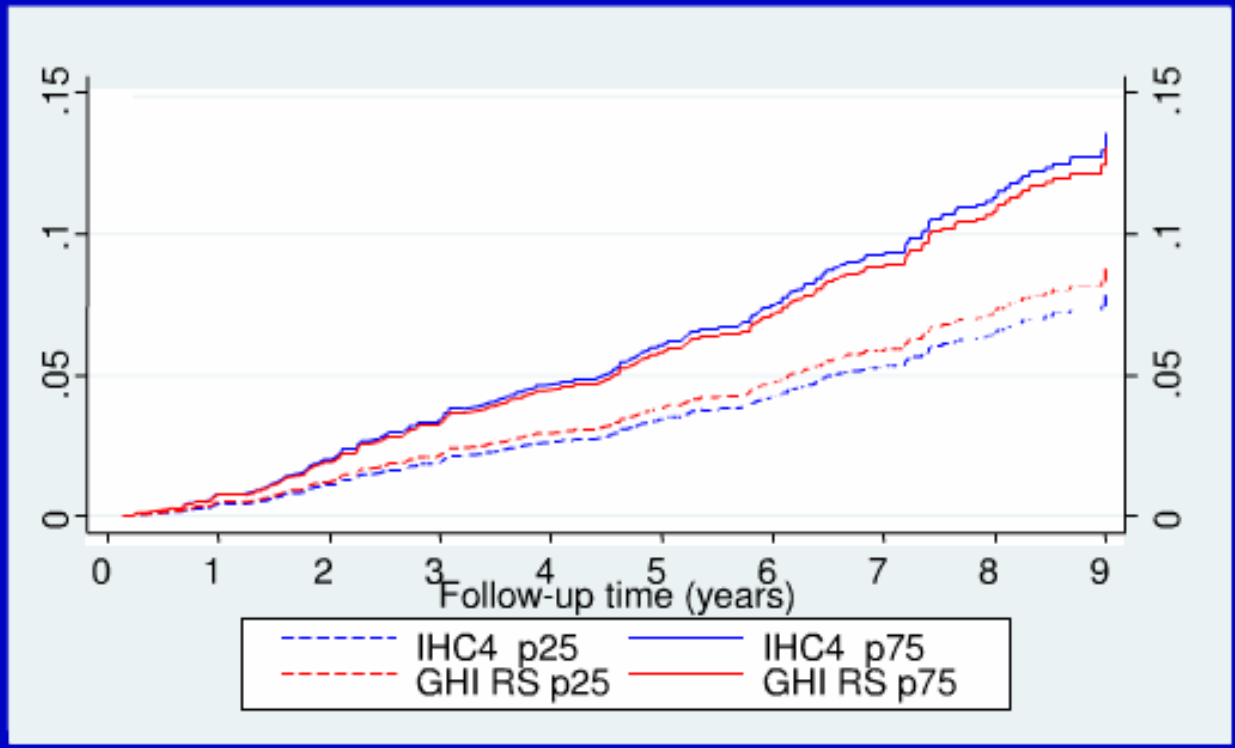
Prognostic Value of a Combined ER, PgR, Ki67, HER2 Immunohistochemical (IHC4) Score and Comparison with the GHI Recurrence Score - Results from TransATAC

Abtract #74

Cuzick J, Dowsett M, Wale C, Salter J, Quinn E, Zabaglo L, Howell A, Buzdar A, Forbes JF. Queen Mary University

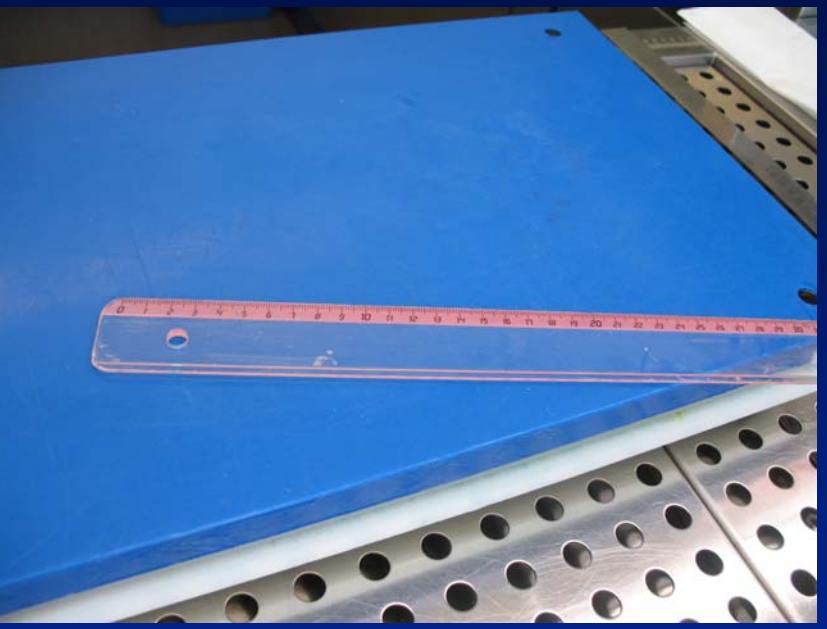
Distant recurrence - predicted values

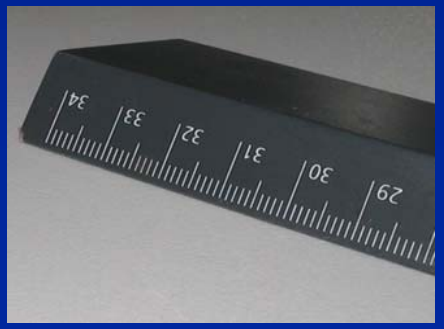
KM curves to 9 yrs with shrinkage adjustment for IHC4 (6.8%) and inflation of GHI-RS (12.2%)



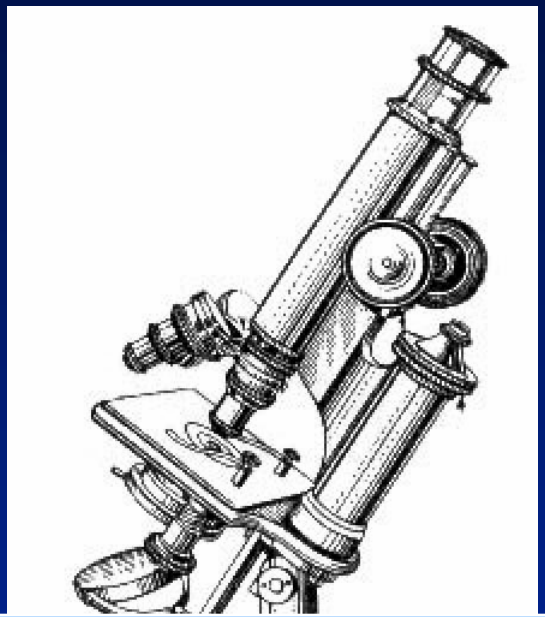
IHC4=ER / PR / HER2 /Ki67

Tumor size measurement





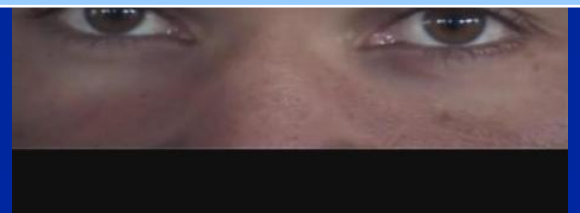
Assessment of differentiation grade, ER, PR, HER2



Interobserver variation grade ~ 30%

Different AOL risk group in 8%

Bueno-de-Mesquita et al. Ann Oncol 2009

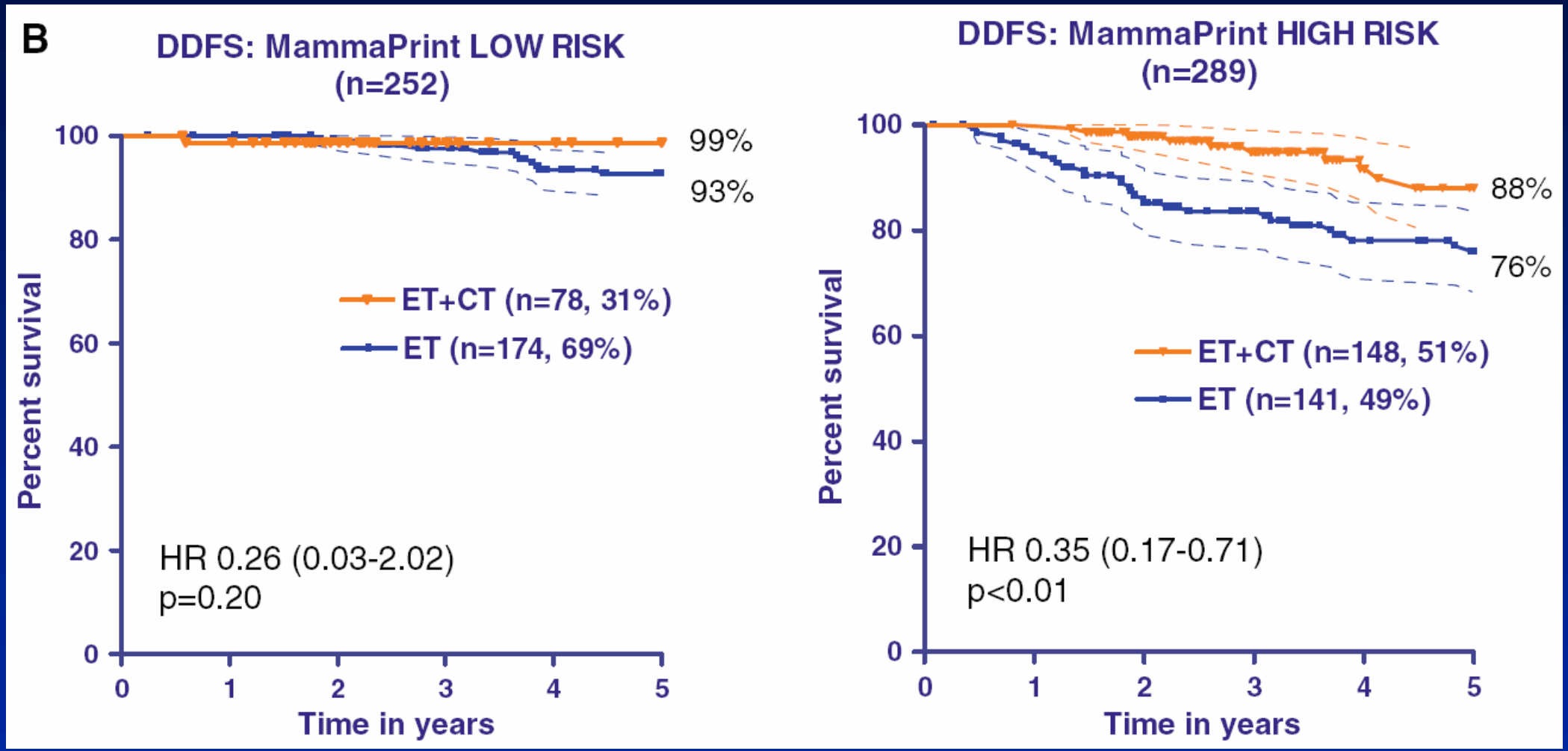


Advantage gene expression classifiers

More reproducible than pathologists

No interobserver variation

Mammaprint predictive for chemotherapy benefit?



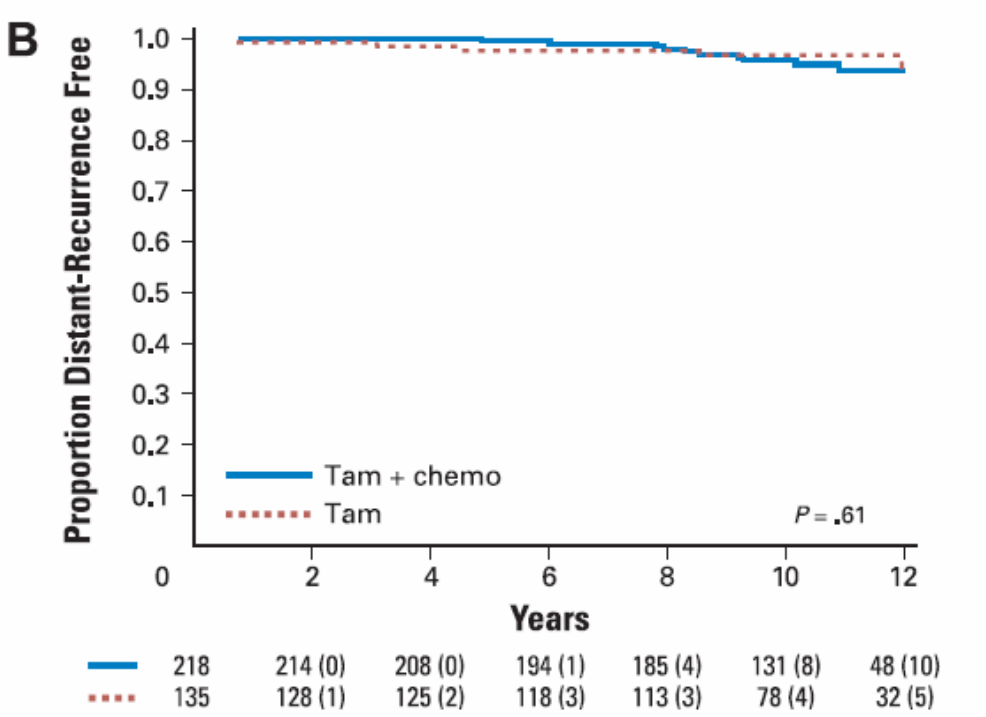
Test for interaction P=NS

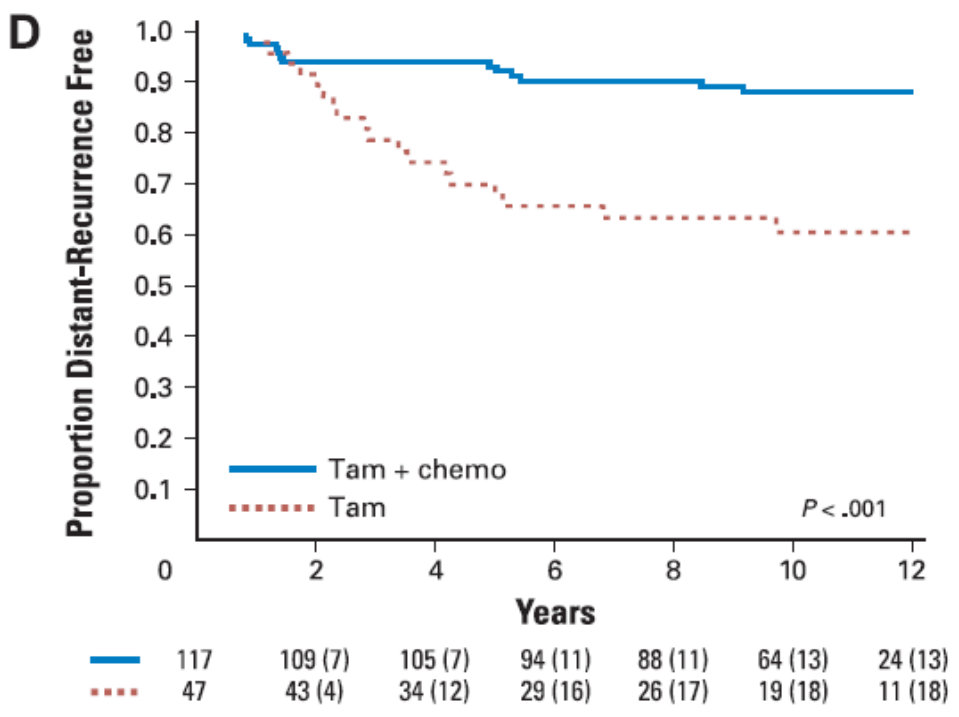
Knauer et al. Breast Cancer Res Treat 2010

Oncotype DX predictive for chemotherapy benefit?

Low recurrence score

High recurrence score



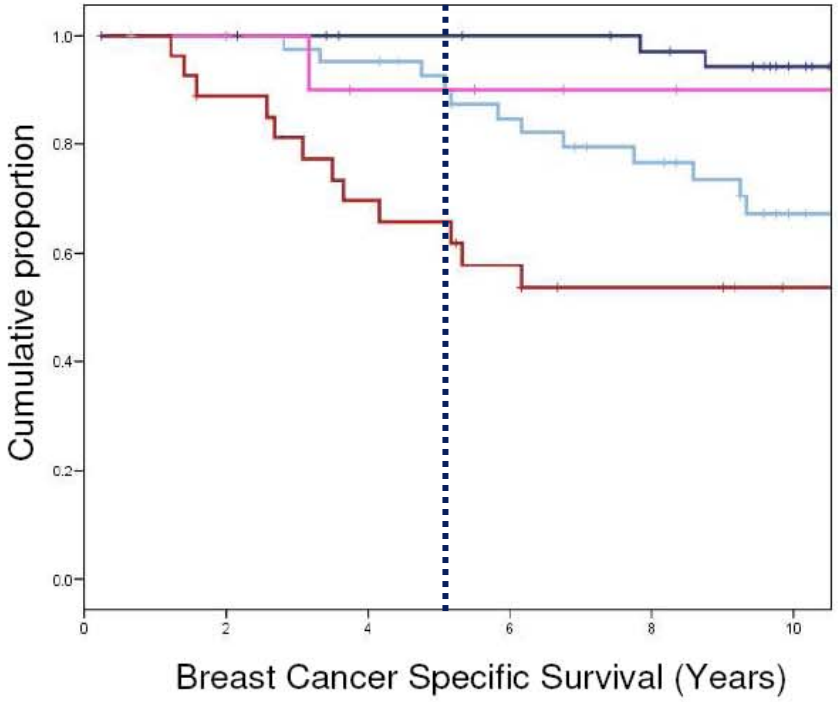


Test for interaction P< 0.05

Paik, JCO 2006

Mammaprint predictive for tamoxifen benefit?

C. 70-gene signature & Endocrine Responsiveness (ER and PR IHC)*



No. at Risk	41	40	37	36	34	26	HR=7.05, 95% CI 1.57-31.5, p=0.011
	42	41	39	32	27	16	
	11	10	8	7	6	5	HR=5.54, 95% CI 0.72-42.65, p=0.10
	27	23	18	14	10	7	

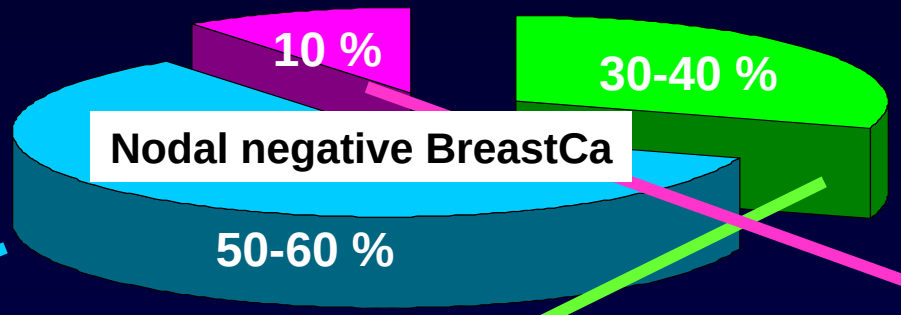
Good risk, incomplete endocrine responsive:

10-yrs BCSS 67%

120 postmeno, all TAM

Kok et al. submitted

TailorX (n=10.500) and MINDACT (n=6.000)



high-risk OncotypeDX
or
high-risk MammaPrint
+
high-risk Adjuvant!

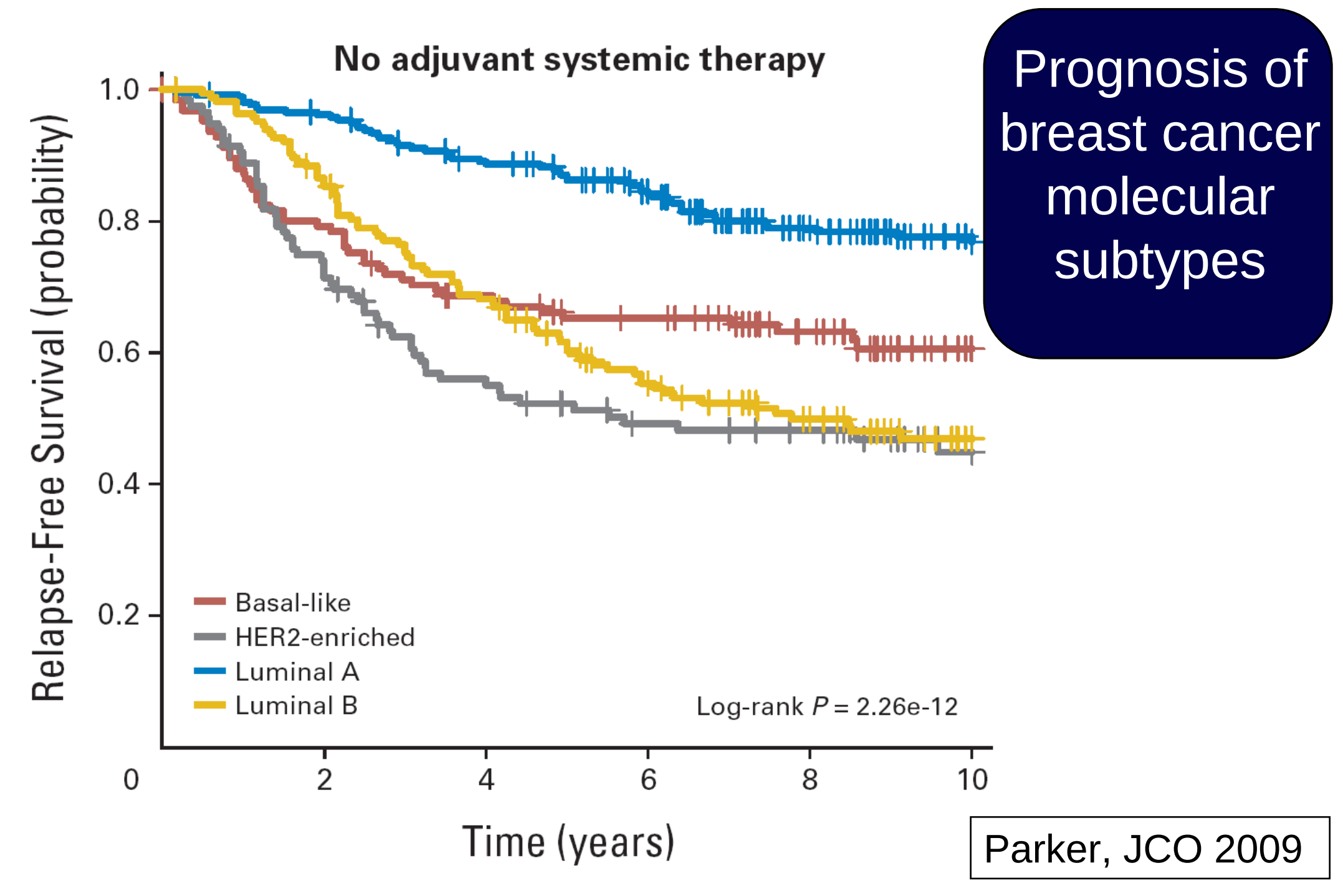
intermediate risk Oncotype DX
or
Discordant groups
(low-risk MammaPrint
and
High-risk Adjuvant!

low-risk OncotypeDX
or
low-risk Mamma
+
low-risk Adjuvant!

Chemo

Random: CTX yes/no (TailorX)
Random: Decision-Tool (MINDACT)

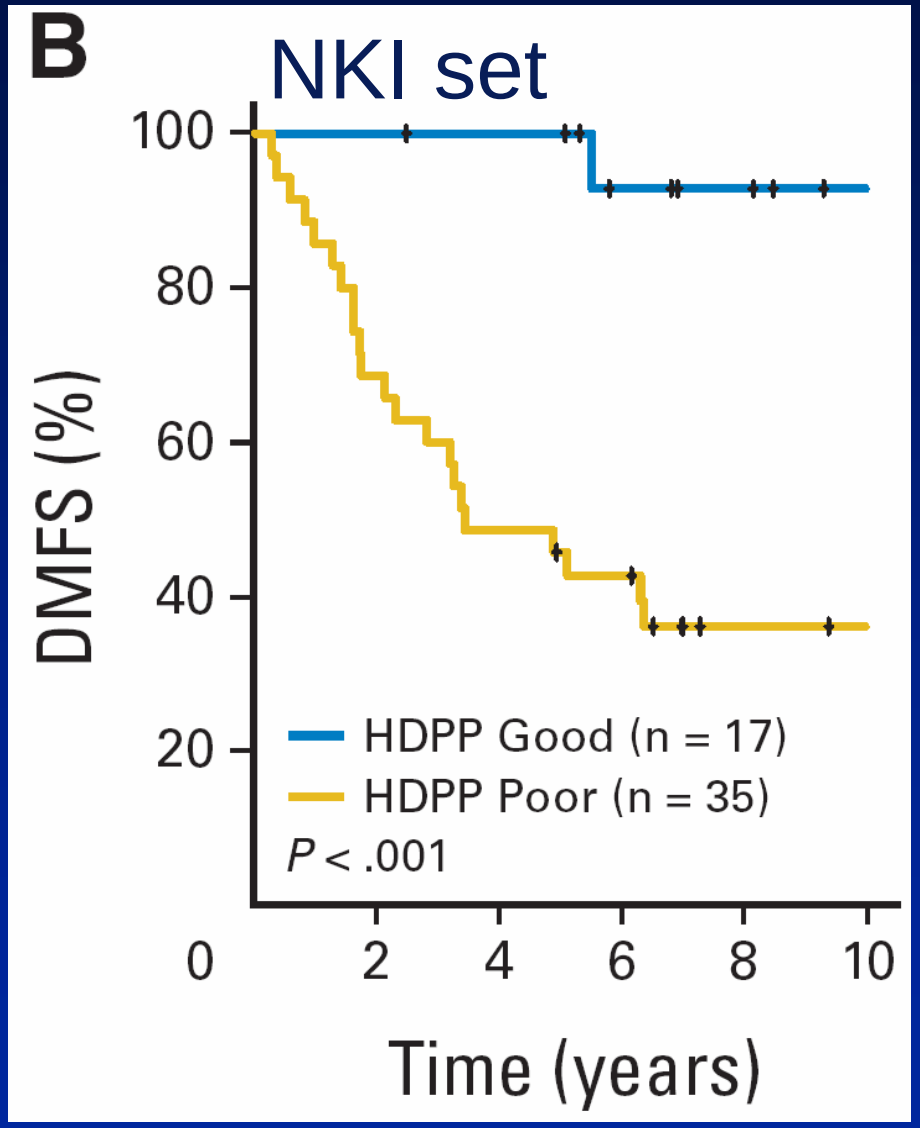
endocrine

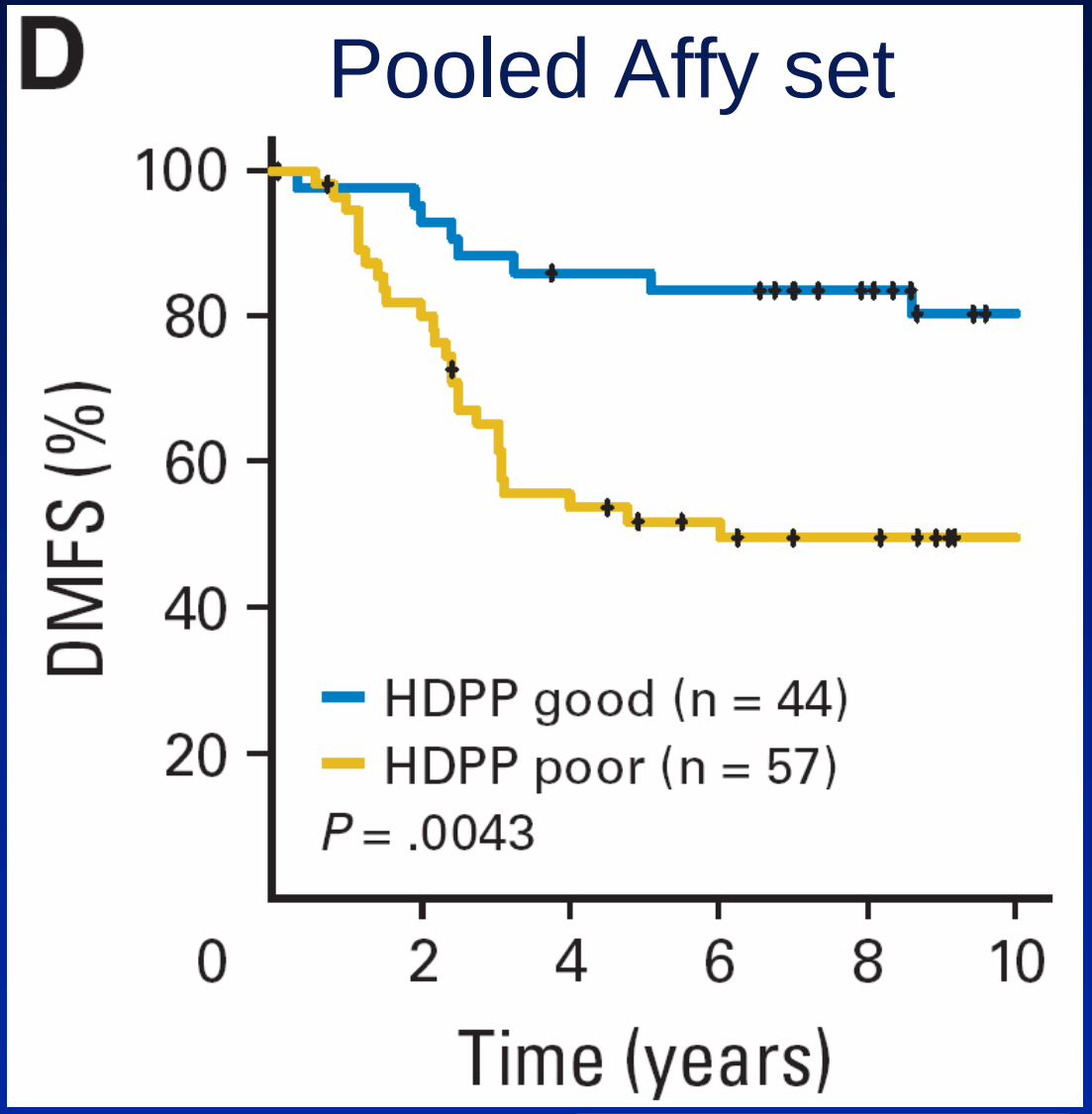


Prognosis of breast cancer molecular subtypes

Parker, JCO 2009

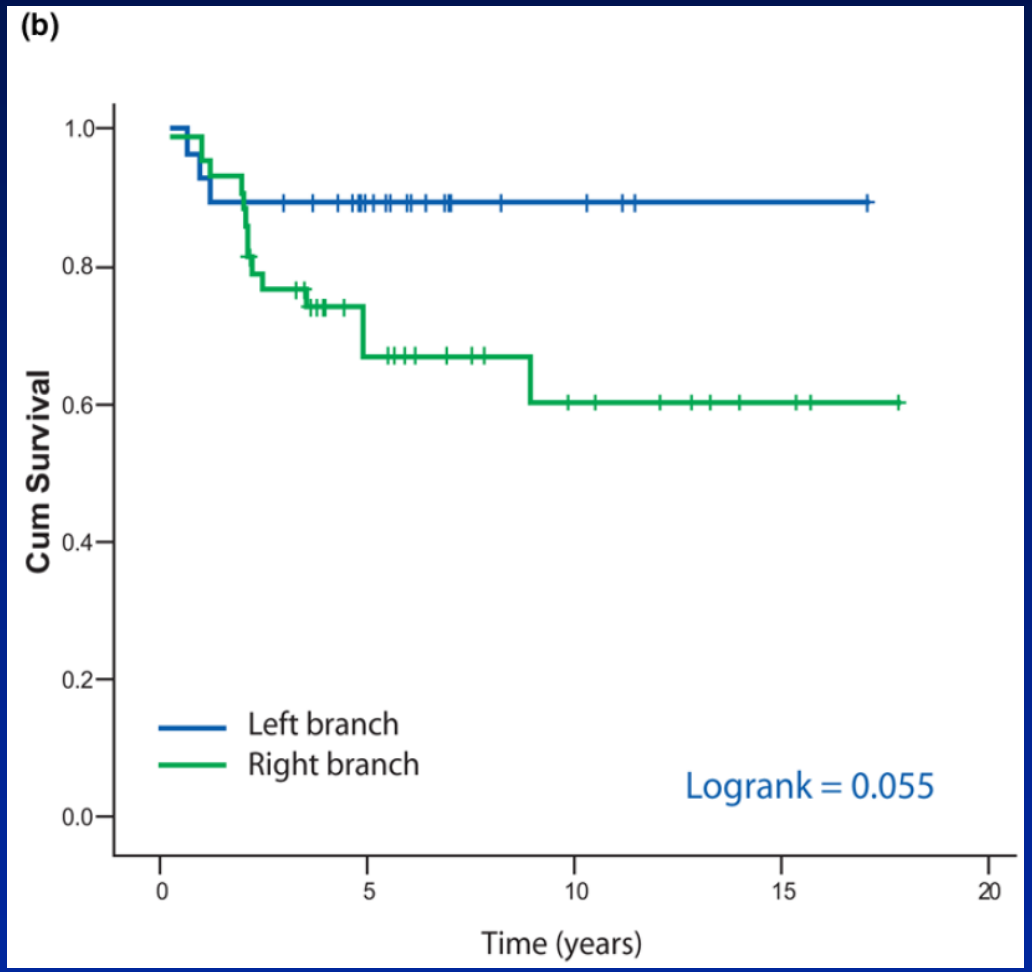
Prognostic classifier for HER2 positive BC

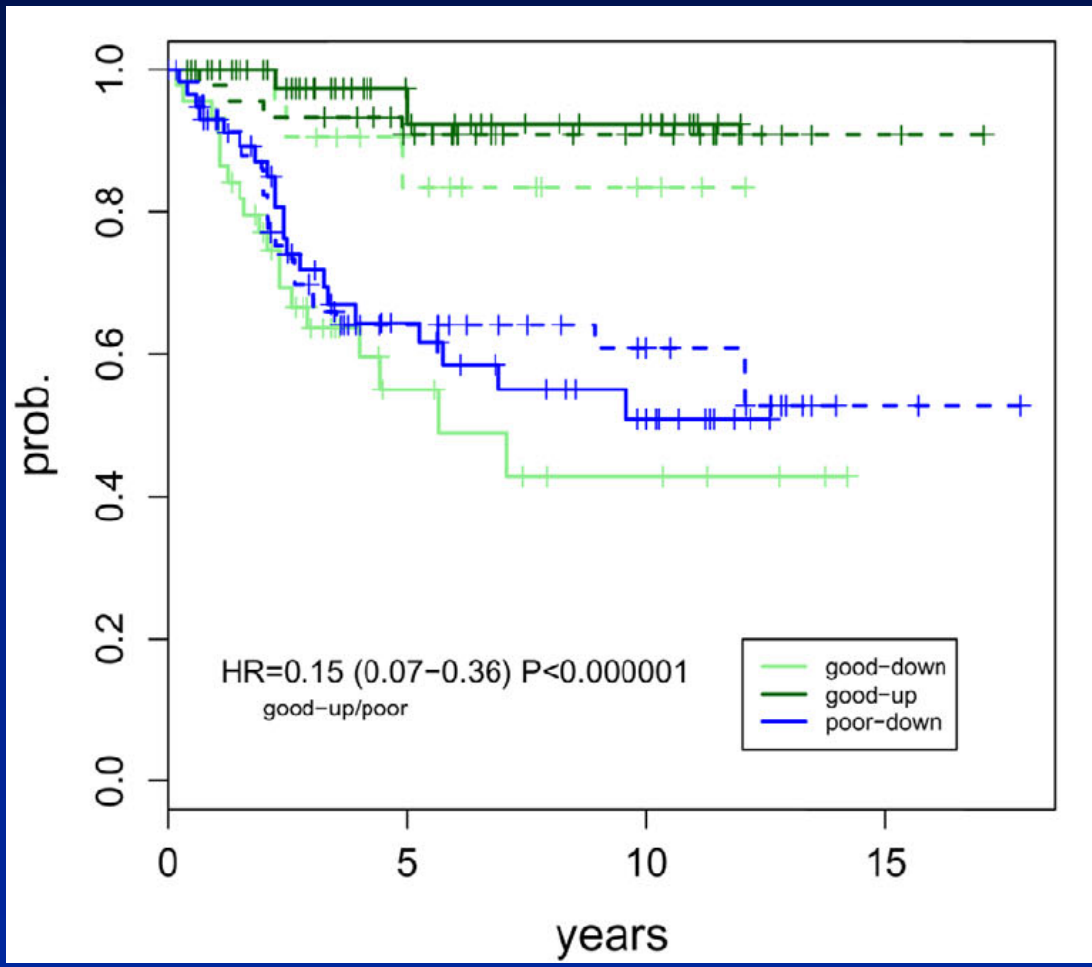




Staaf, JCO 2010

Prognostic classifier for triple negative BC





Kreike, Breast Cancer Res, 2007

Teschendorff, Breast Cancer Res, 2008

Prognostic classifier for ER pos PR neg BC

Work in progress….

Response prediction

- Is the target of the drug present in the cancer cells and is this target the ‘Achilles heel’ of these cancer cells?

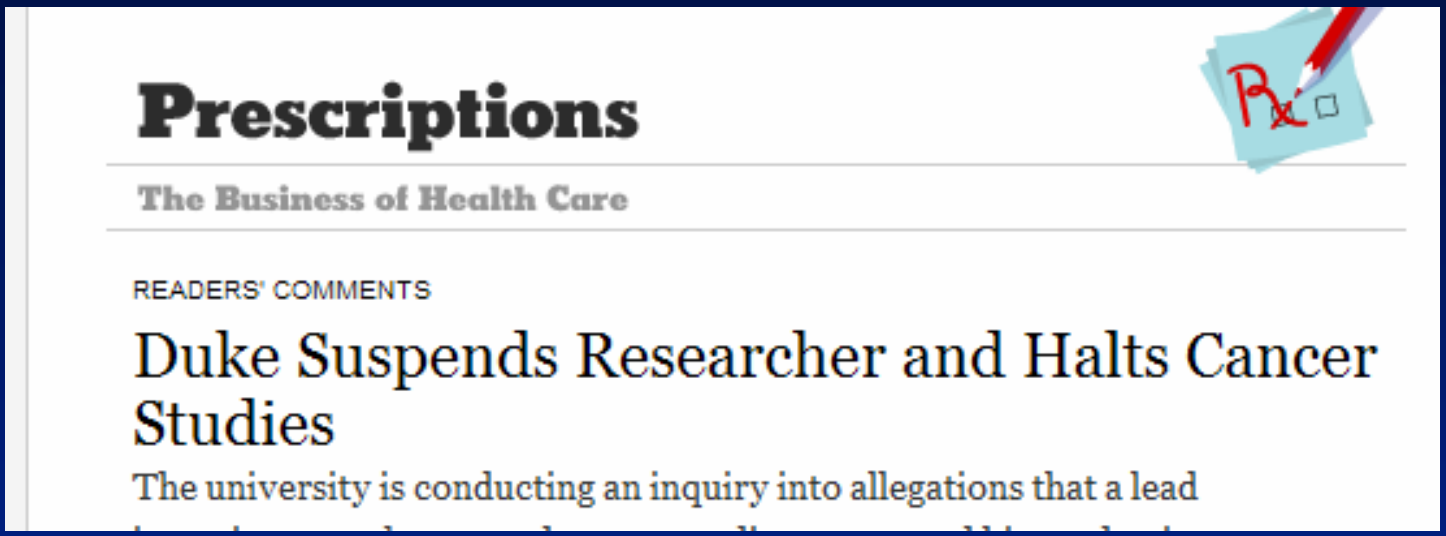
Predictive classifier for paclitaxel benefit

Assessment of an RNA interference screen-derived mitotic and ceramide pathway metagene as a predictor of response to neoadjuvant paclitaxel for primary triple-negative breast cancer: a retrospective analysis of five clinical trials

Nicolai Juul, Zoltan Szallasi*, Aron C Eklund*, Qiyuan Li, Rebecca A Burrell, Marco Gerlinger, Vicente Valero, Eleni Andreopoulou, Francisco J Esteva, W Fraser Symmans, Christine Desmedt, Benjamin Haibe-Kains, Christos Sotiriou, Lajos Pusztai, Charles Swanton*

Lancet Oncol, 2010;11:358-365

The Anil Potti drama



Prescriptions

The Business of Health Care

READERS' COMMENTS

Duke Suspends Researcher and Halts Cancer Studies

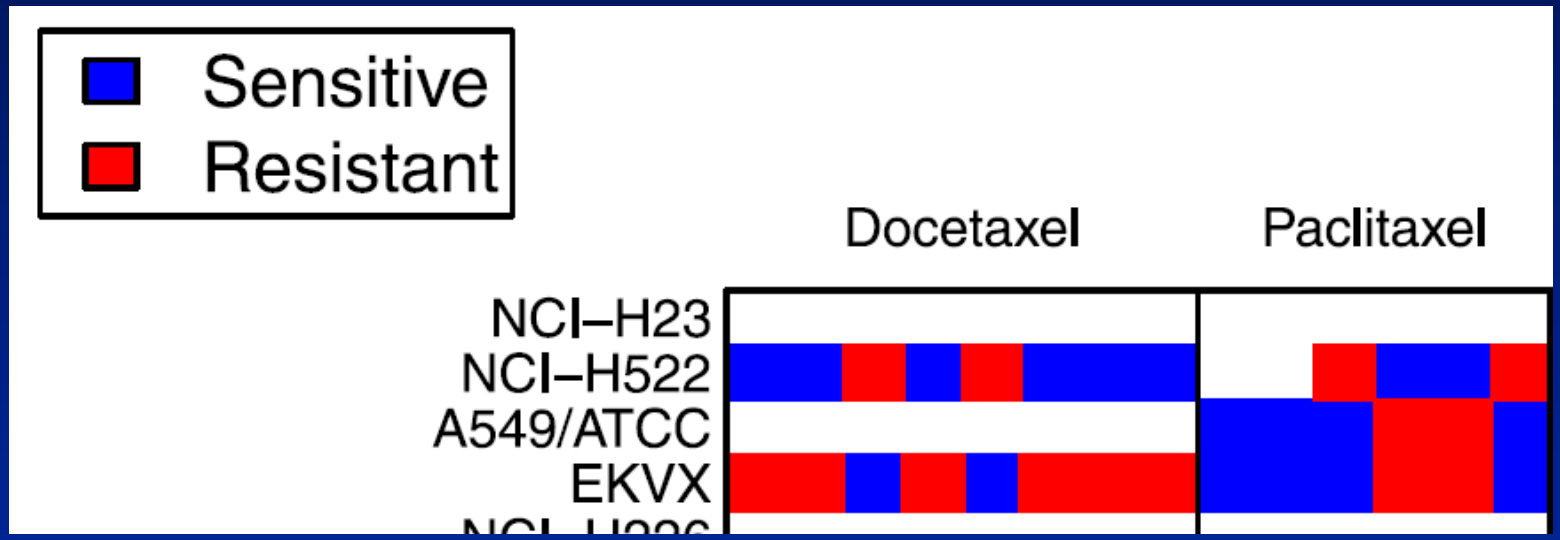
The university is conducting an inquiry into allegations that a lead

Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial

Hervé Bonnefoi, Anil Potti, Mauro Delorenzi, Louis Mauriac, Mario Campone, Michèle Tubiana-Hulin, Thierry Petit, Philippe Rouanet, Jacek Jassem, Emmanuel Blot, Véronique Becette, Pierre Farmer, Sylvie André, Chaitanya R Acharya, Sayan Mukherjee, David Cameron, Jonas Bergh, Joseph R Nevins, Richard D Iggo

The Anil Potti fraud

Cell lines switch label in different studies



Paper 1 2 3 4 5

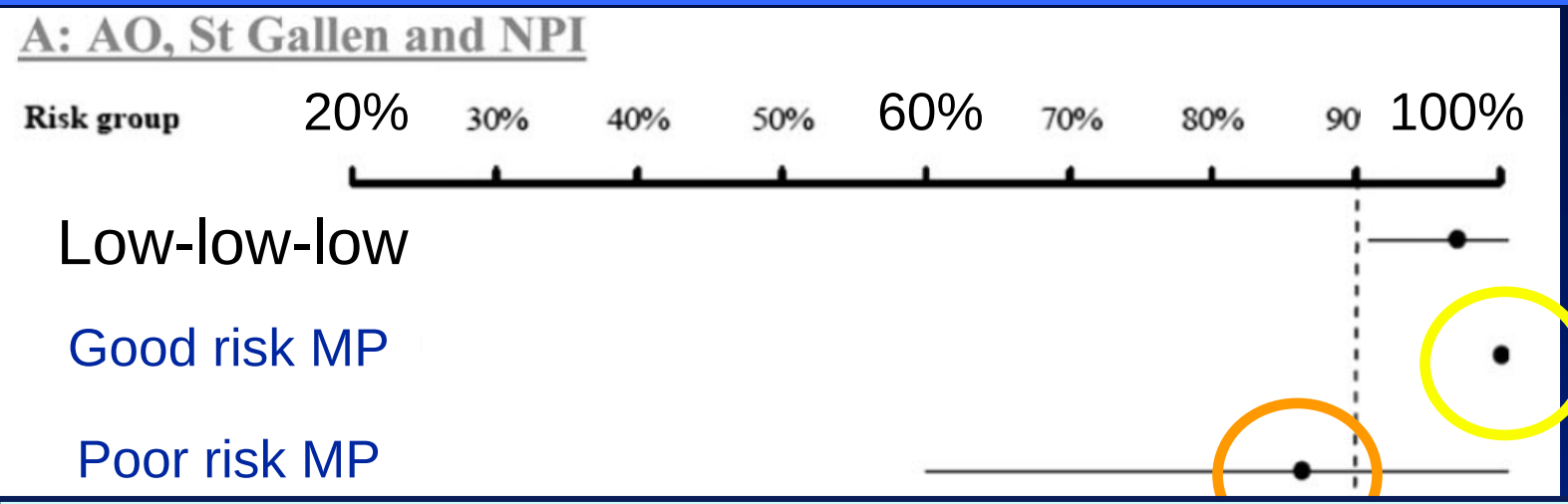
Baggerly & Coombes, Ann Appl Stat 2009

Take home messages

- Prognostic gene expression classifiers should add information to conventional prognostic markers (ROC curves – AUC) to be clinically useful
- Most prognostic classifiers are driven by proliferation and estrogen response clusters
- Most important advantage; reproducibility
- Prognostic classifiers for defined molecular and histological subgroups are the future
- The immune response module and genes associated with metastatic potential dominate prognostic classifiers for HER2 pos and triple neg breast cancer
- Suspect predictive classifiers without a mechanistic explanation for anticancer drug (in)activity

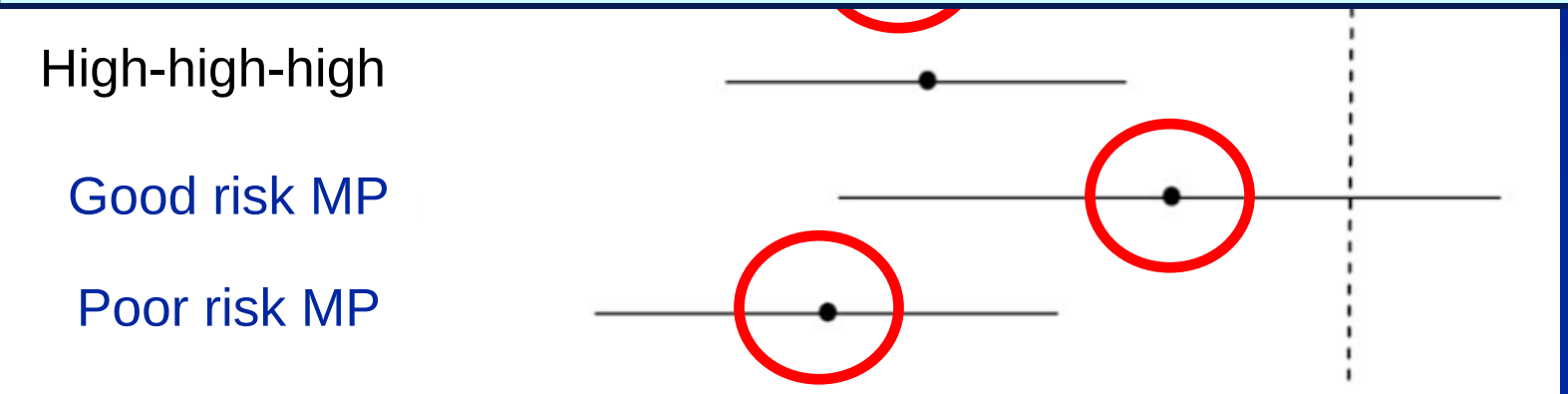

Thank you for your attention

Combine clinical risk indexes and Mammaprint



10-yrs OS

High AO / high St Gallen / high NP; MP low risk should still receive chemotherapy + endocrine therapy



Bueno-de-Mesquita, Ann Oncol 2009