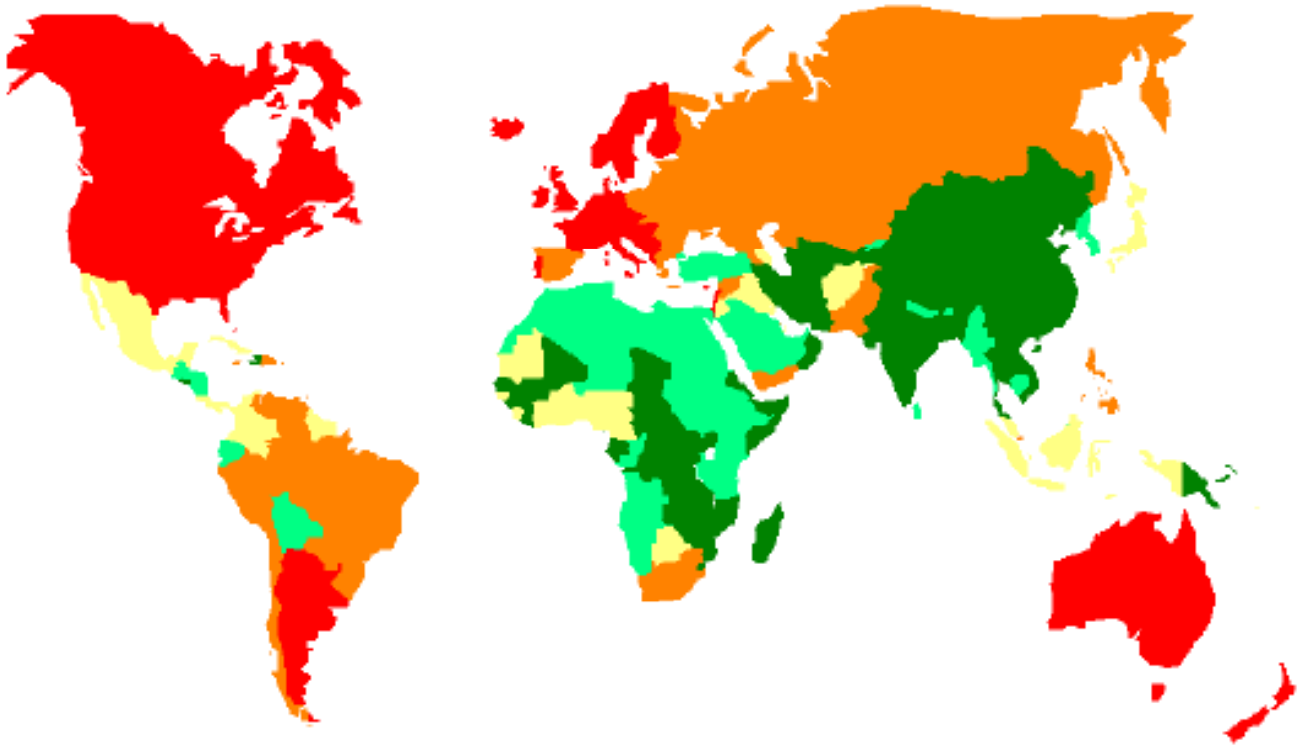
An epidemiological perspective on the causes and prevention of breast cancer

Valerie Beral MD, FRS
University of Oxford, UK

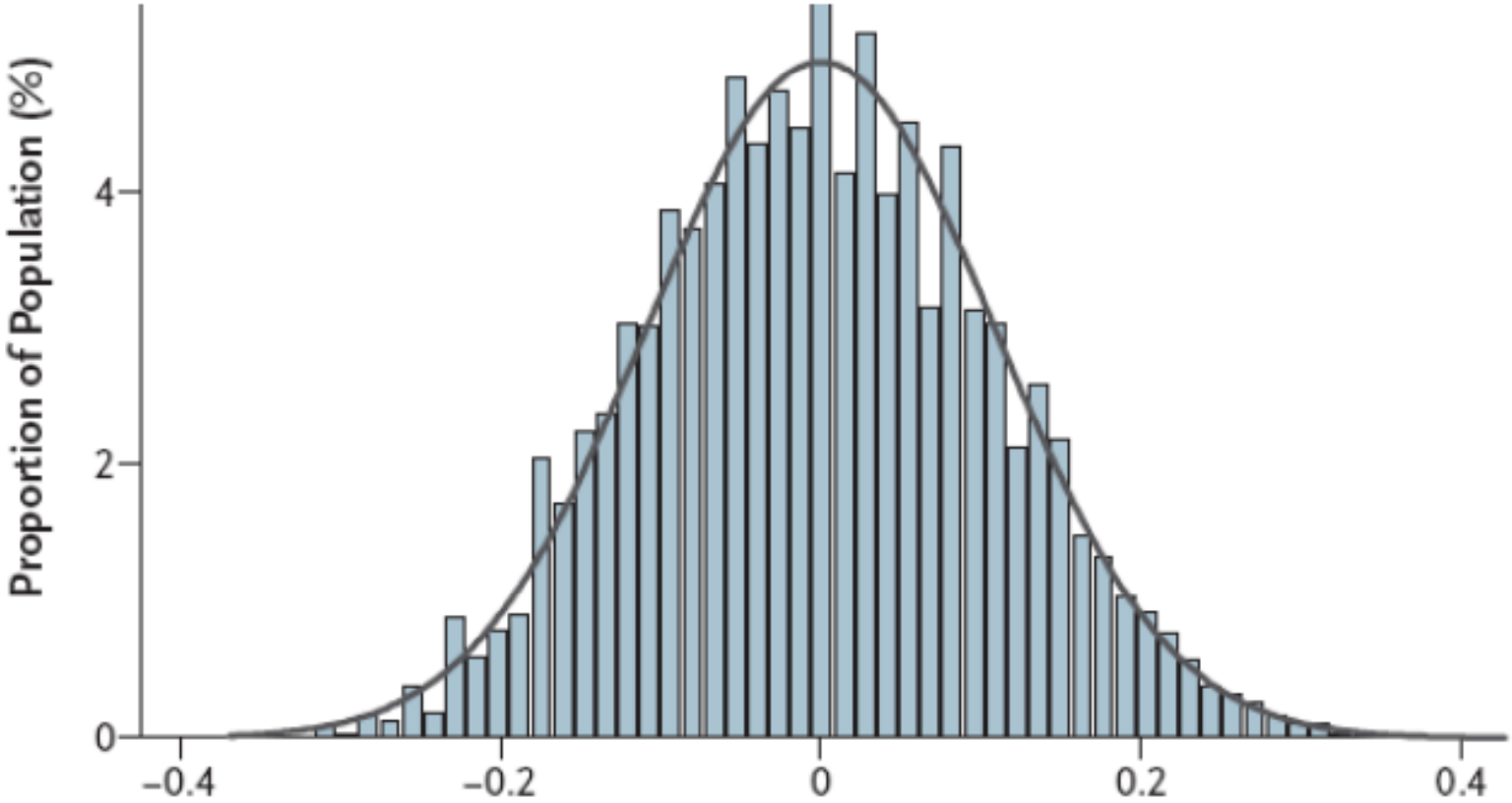


Source: WHO/ IARC

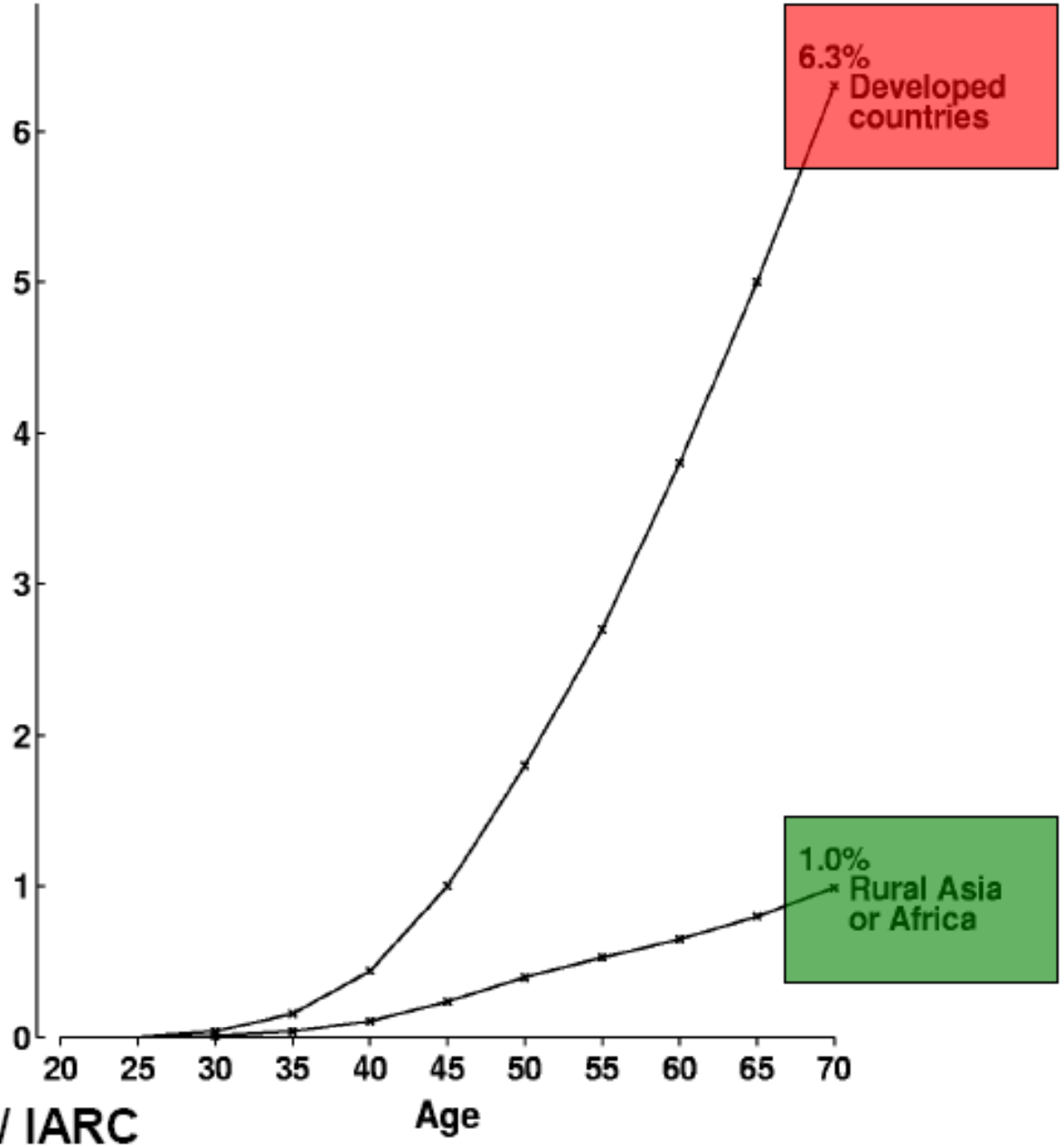
low incidence high incidence

Polygenic breast cancer risk from 7 SNPs

(Pharoah et al NEJM, 2008)



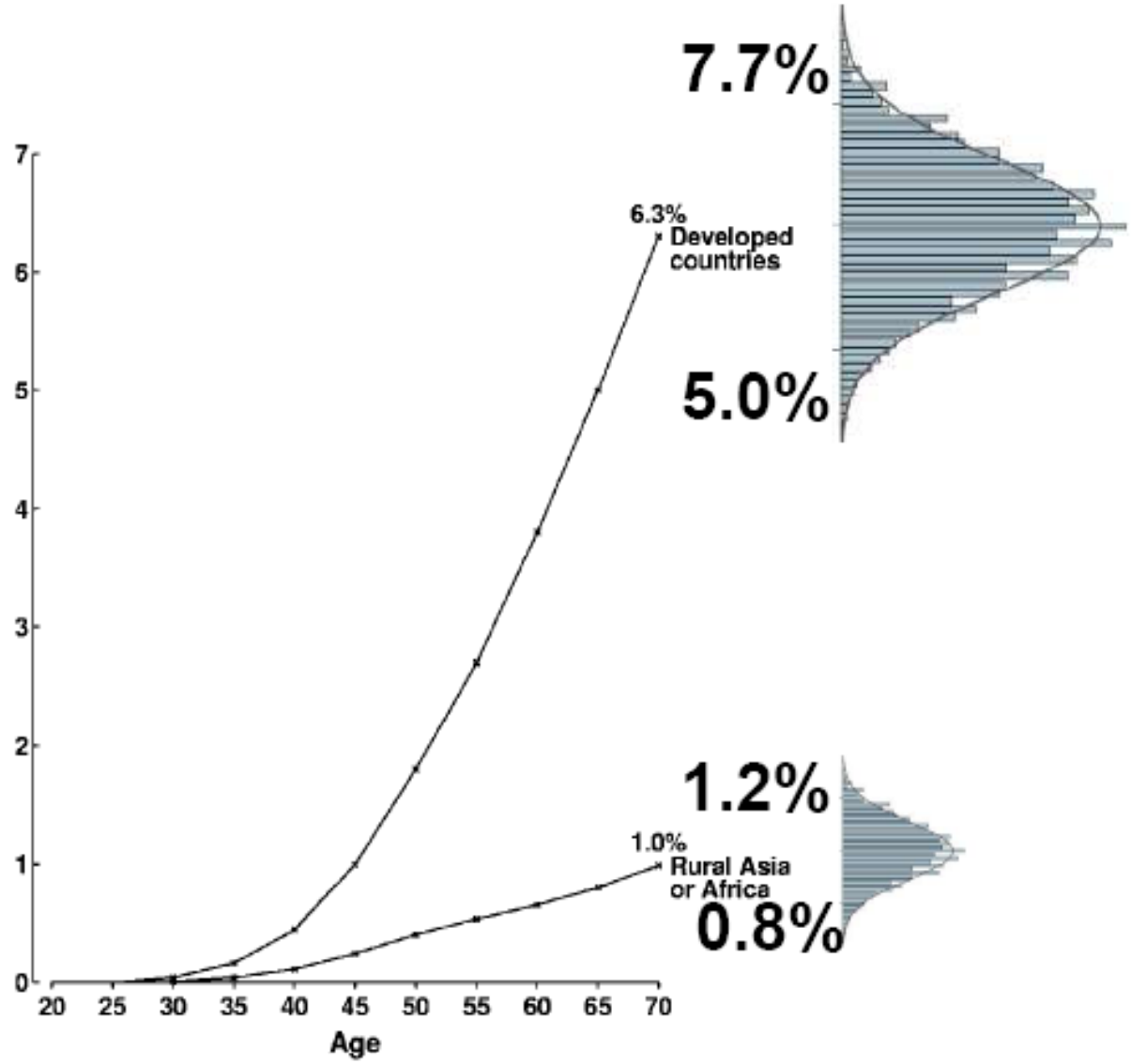
Cumulative incidence of breast cancer (%), by age



Source: WHO/ IARC

Polygenetic risk cannot determine who will and who will not develop breast cancer

Few women in developed countries are at low risk of breast cancer

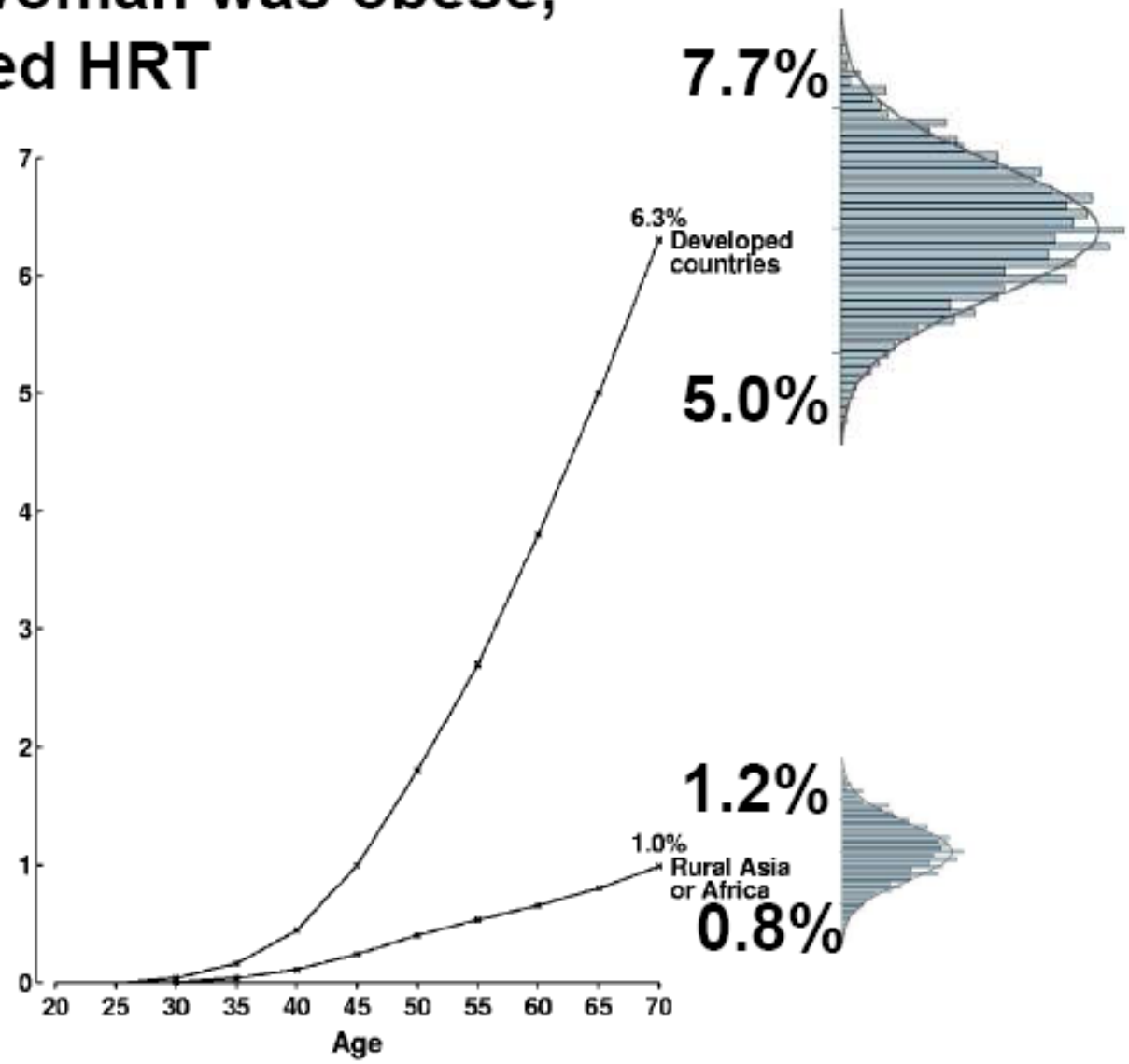


Preventing breast cancer

the main modifiable cause is childbearing

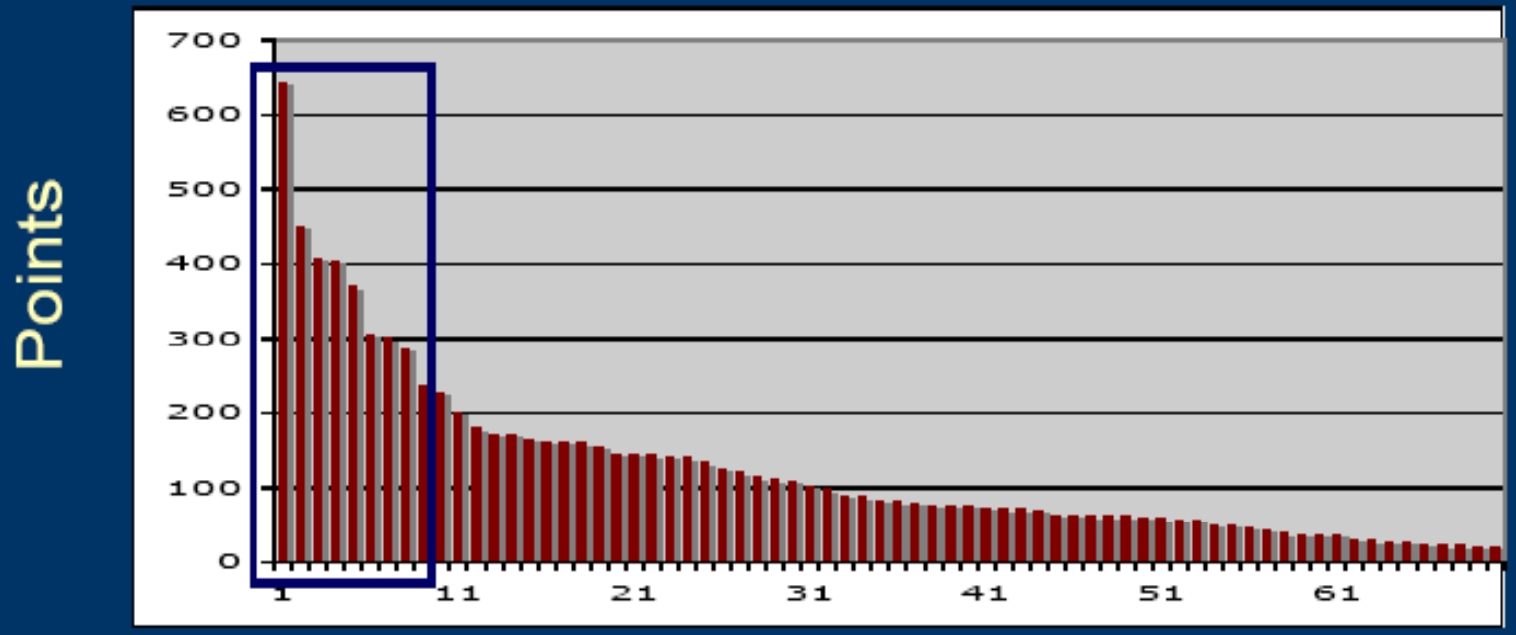
but altering childbearing patterns is not a realistic option, so interventions mimicking the effects of childbearing and lactation are needed

Modifiable factors in the USA:
180,000 breast cancers/year would be
~40,000 fewer if no woman was obese,
drank alcohol, or used HRT



Few women in developed countries are at low risk of breast cancer

‘Top-Ten’ : The Most Important Translational Breast Cancer Research Questions



- First: Identification of molecular signatures to select patients on endocrine therapy who could be spared chemotherapy (643 points from 430 specialists).

Dowsett, Goldhirsch et al Breast Cancer Res. 2007

Combining genomic profiling (70 gene-mammaprint) with nodal status allows to classify patients with primary breast cancer and positive lymph nodes (1-9) into very distinct prognostic subgroups that could help tailor treatment strategies

M. Saghatchian[1], S. Mook[2], G. Pruneri[3], G. Viale[3], A. Glas[4], I. Eekhout[2], S. Delaloge[1], L. van't Veer[2].
[1]Institut Gustave Roussy, Breast Cancer, Villejuif, France.[2]Netherlands cancer institute, Pathology, Amsterdam, The Netherlands.
[3]European Institute of Oncology, EIO, Milan, Italy.[4]Agendia, BV, Amsterdam, The Netherlands

Distance metastases as first event and breast cancer specific survival according to LN group (PN) and genomic profile (MP) are shown in Figures 1 and 2.

Figure 1.

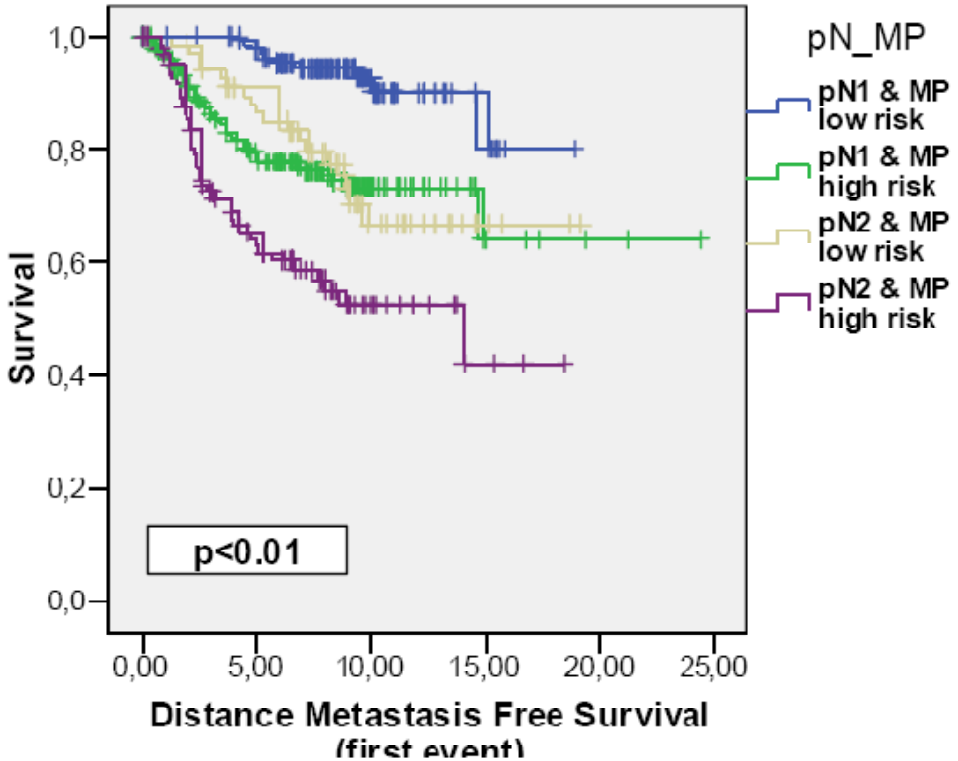
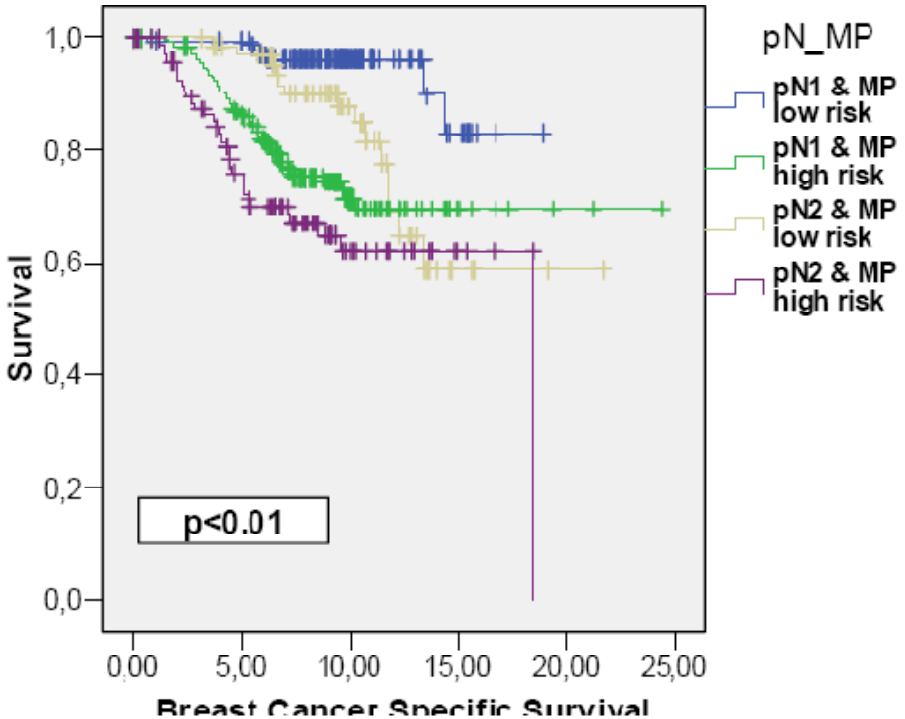


Figure 2.

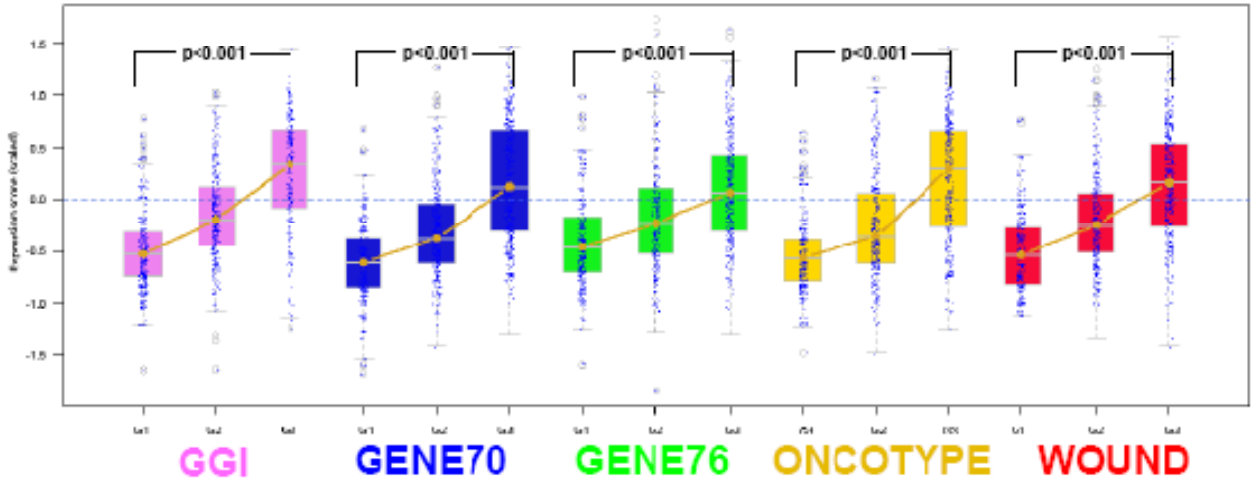


Limited clinical utility of prognostic gene expression profiles in Grade 3 node negative early stage breast cancer

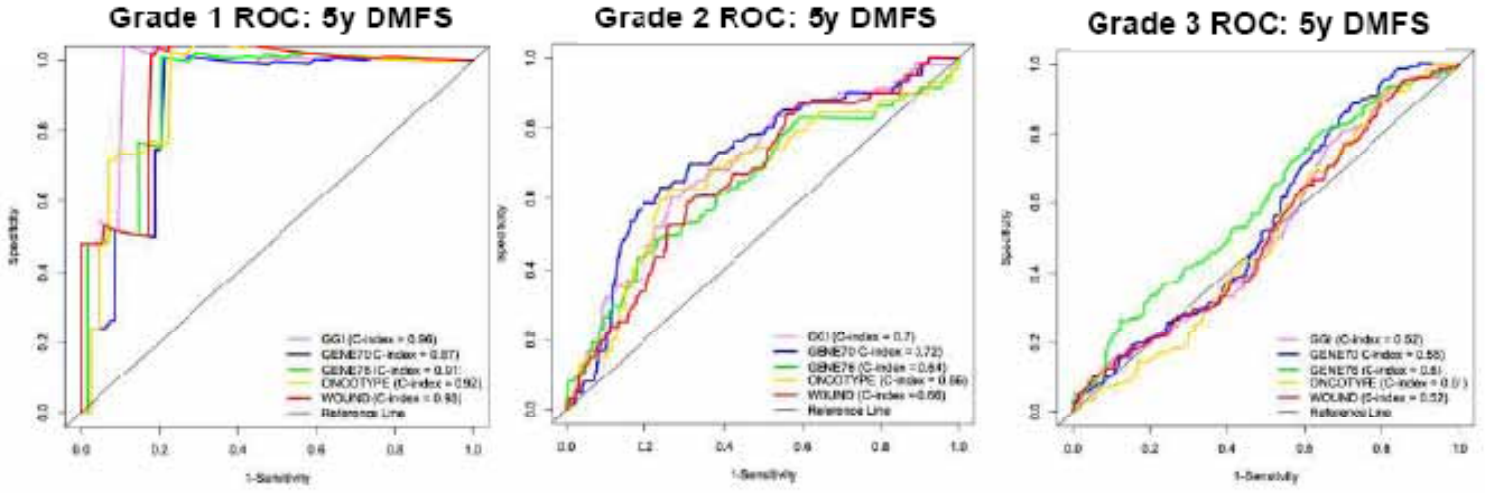
PL Bedard[1], M Ignatiadis[1], B Haibe-Kains[1,2], SK Singhal[1,2], S Loi[1], C Criscitiello[1], C Desmedt[1,2], G Bontempi[2], MJ. Piccart[1,2] and C Sotiriou[1,2]

[1]Translational Research Unit, Jules Bordet Institute, Brussels, Belgium; [2]Université Libre de Bruxelles, Brussels, Belgium

Genomic Risk Score Increases with Histological Grade



Prognostic Signatures Perform Poorly for Grade 3 Tumors



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Prognostic Signatures Identify Grade 1 High Risk small ER+ node negative tumors

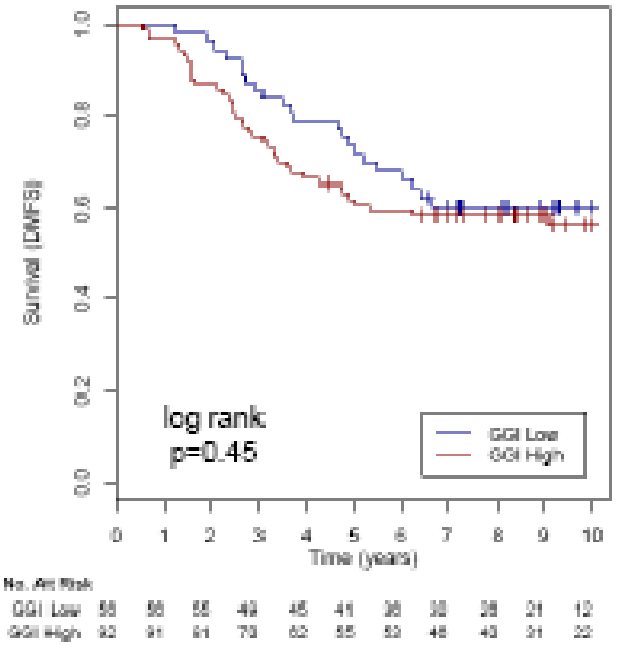
Grade 1 ER+ T≤2cm: GGI

Grade 1 ER+ T≤2cm: GENE70

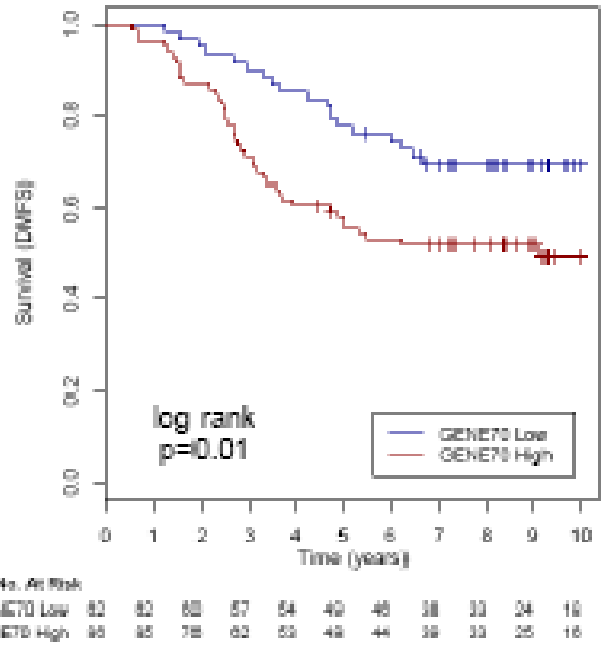
Grade 1 ER+ T≤2cm: GENE76

Prognostic Signatures Do Not Identify Sufficiently Low Risk Grade 3 small ER+ node negative tumors to avoid Chemo

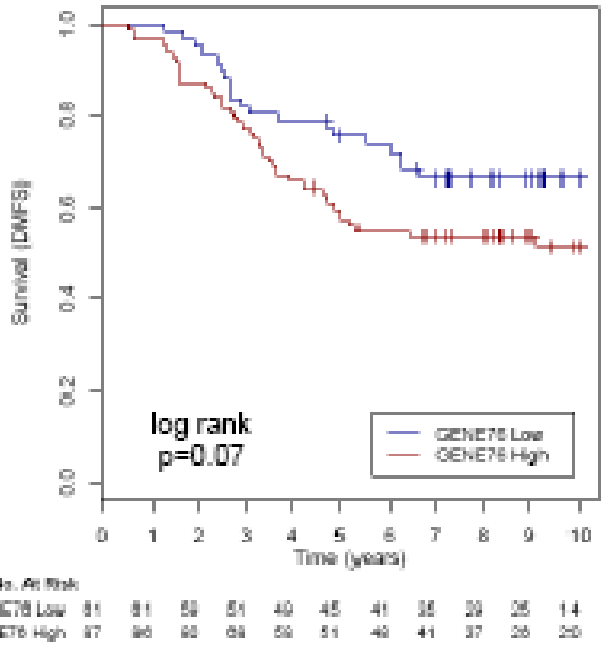
Grade 3 ER+ T≤2cm: GGI

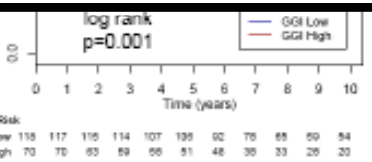


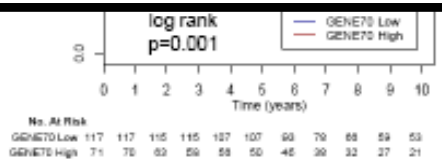
Grade 3 ER+ T≤2cm: GENE70

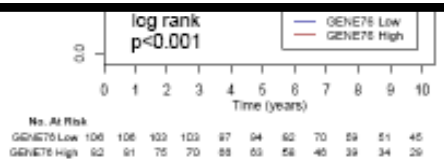


Grade 3 ER+ T≤2cm: GENE76





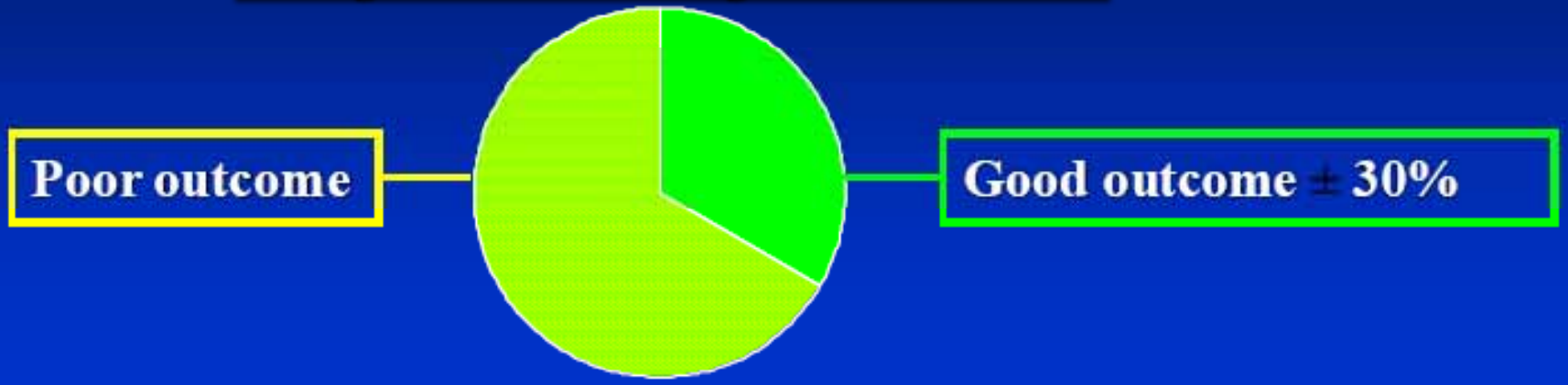




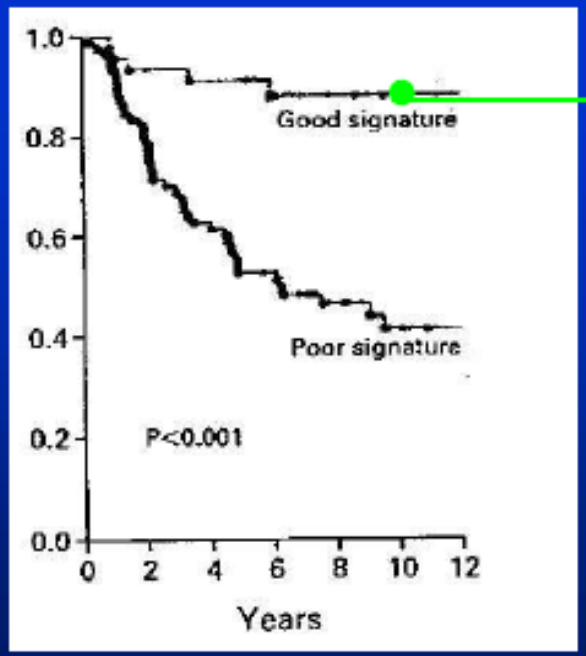
JUDGING THE « CLINICAL UTILITY » OF NEW BIOMARKERS

A) For Prognosis

Background knowledge on the disease

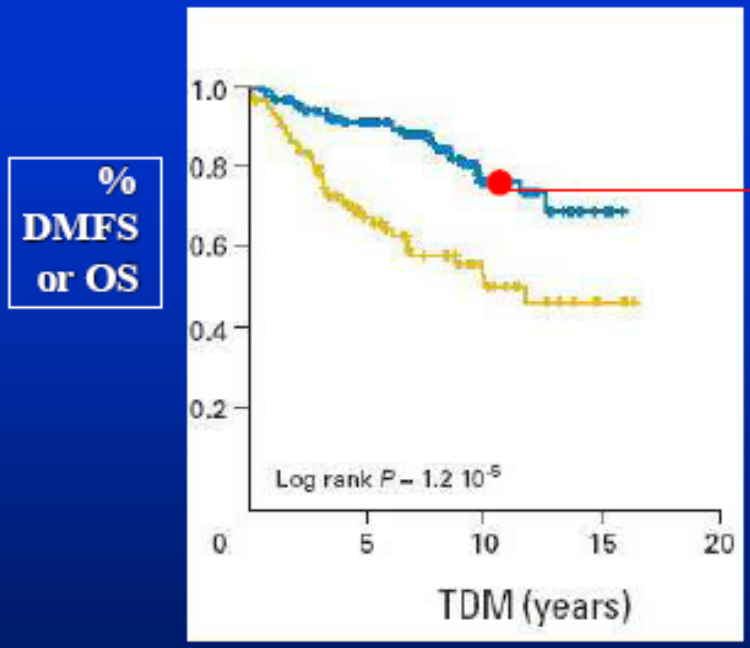


Useful biomarker / gene signature



Excellent outcome and ± 30% of patients!

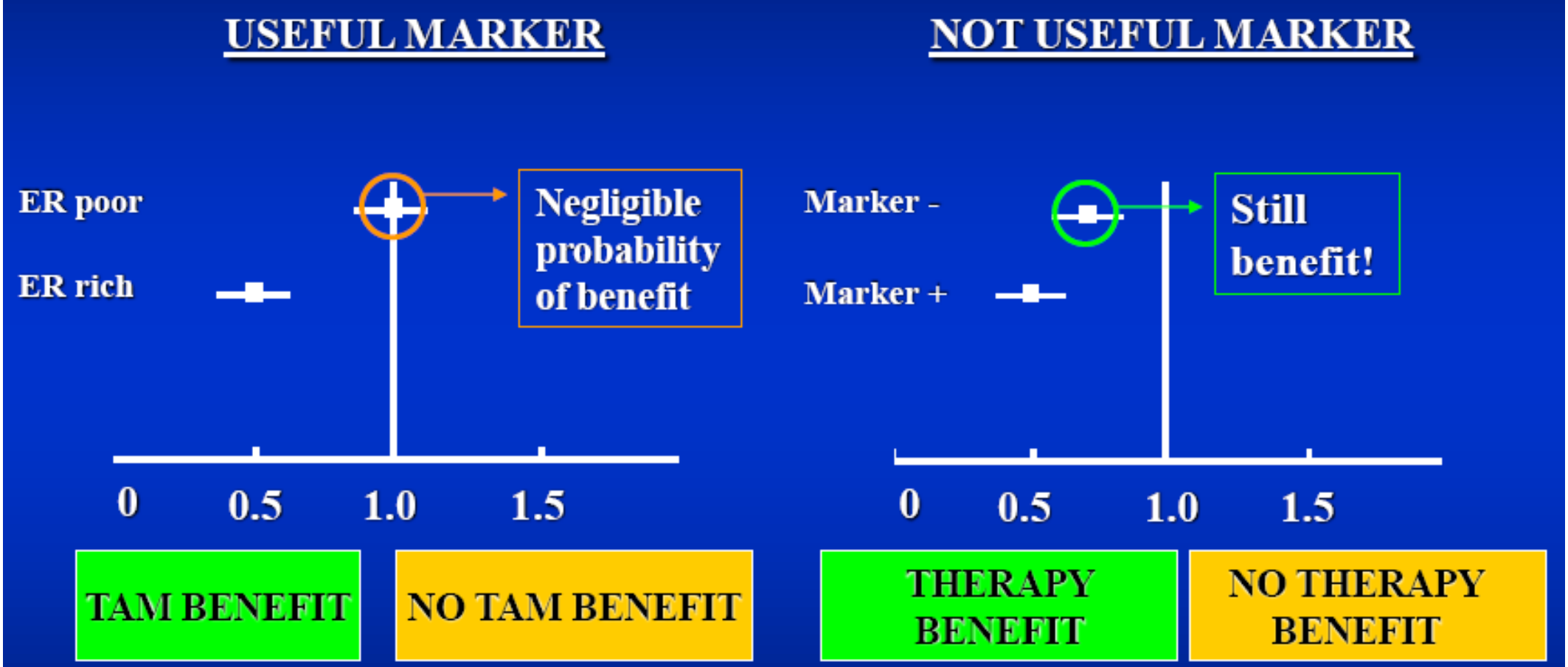
Not useful biomarker / gene signature



Unsatisfacory outcome

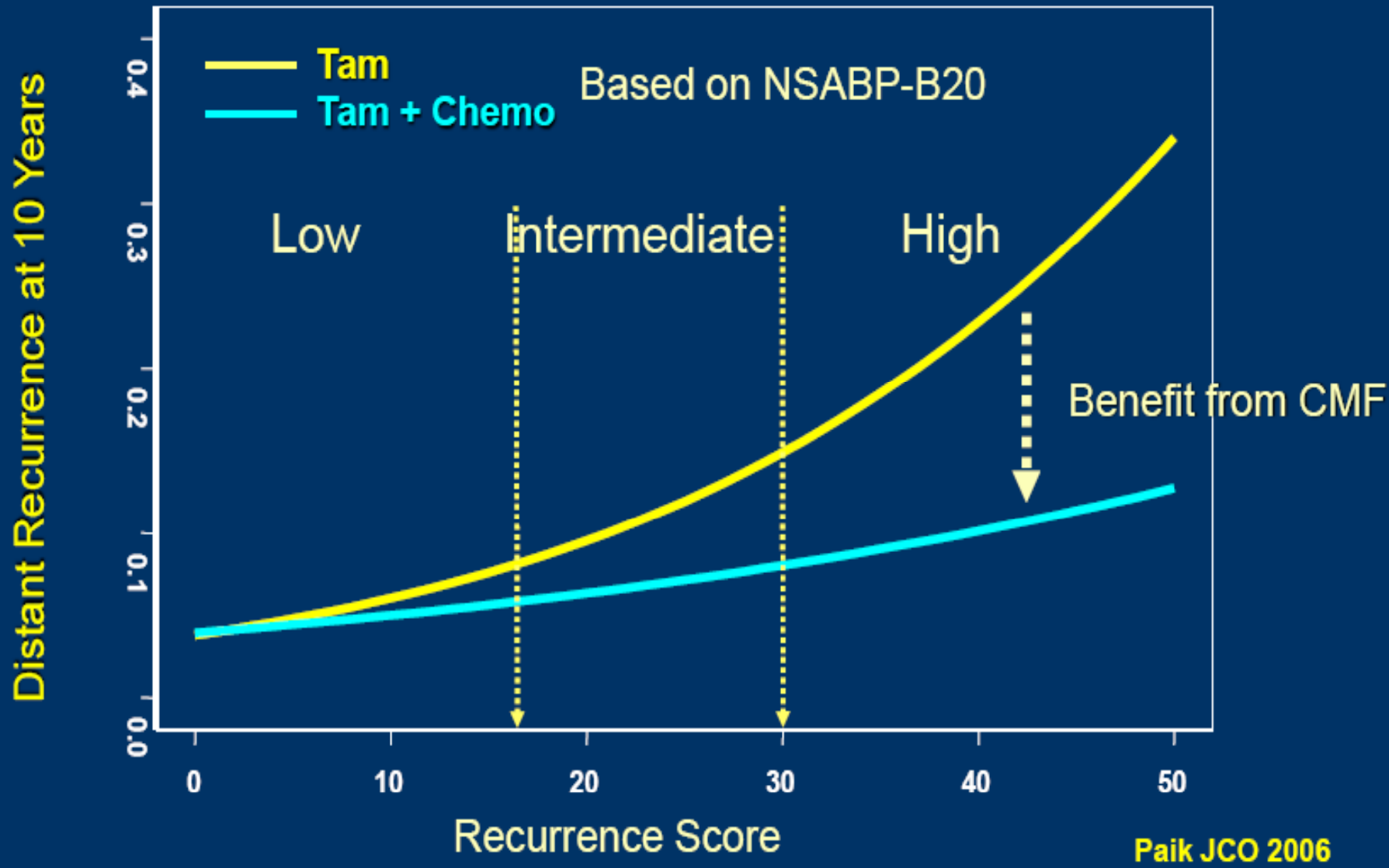
Ideally, there should be a treatment for the poor risk group!

JUDGING THE « CLINICAL UTILITY » OF NEW BIOMARKERS
B) For Prediction of Treatment Efficacy



Why do Clinicians Like GHI-RS (Oncotype Dx)?

Predictive for Chemotherapy Benefit



Paik JCO 2006

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

in postmenopausal breast cancer patients treated with anastrozole or tamoxifen

A TransATAC study

Jack Cuzick

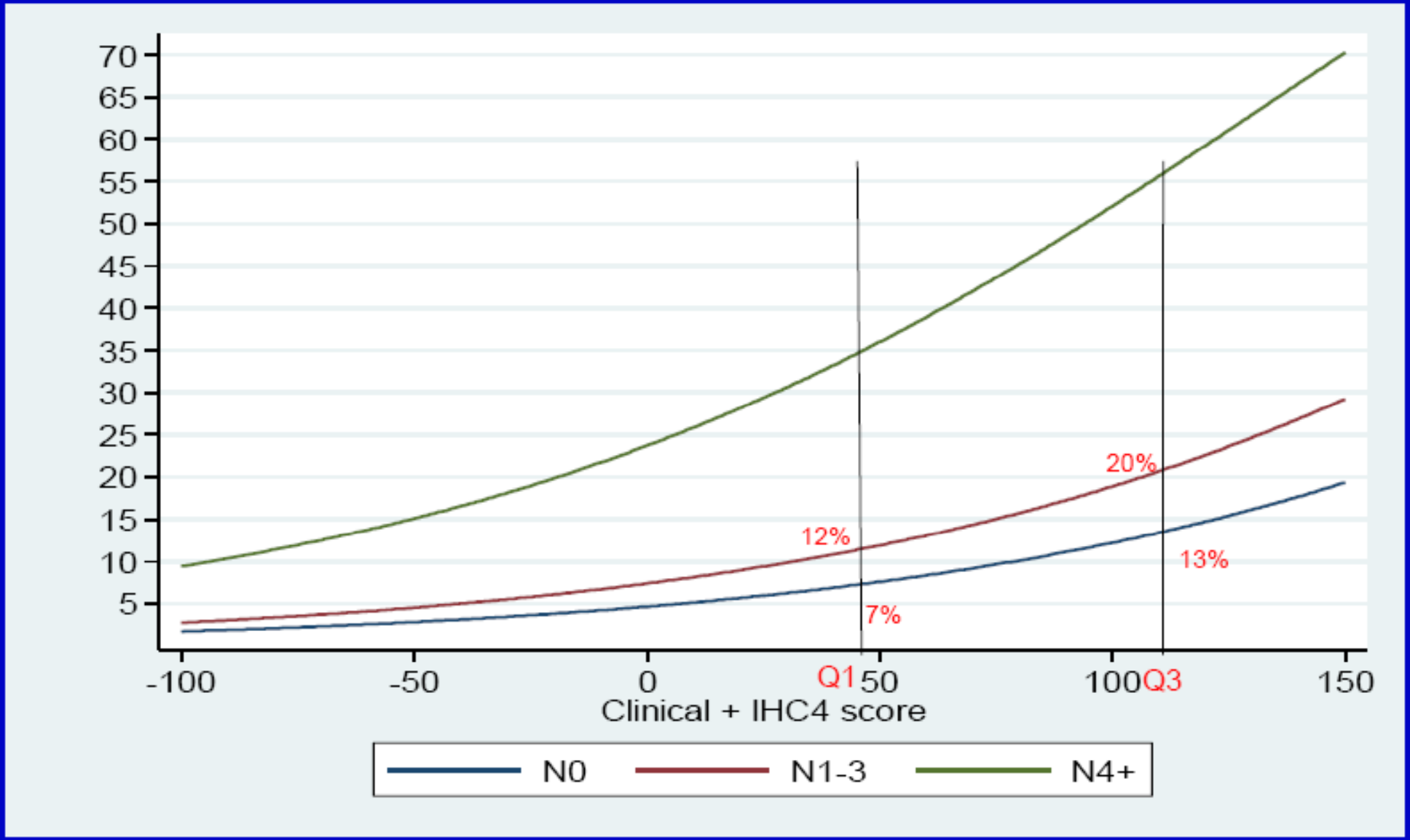
Mitch Dowsett, Chris Wale, Janine Salter, Emma Quinn, Lila Zabaglo, Elizabeth Mallon, Anthony Howell, Aman Buzdar, John Forbes on behalf of the ATAC/LATTE Trialists' Group

Relative Contribution of IHC4 components

$\Delta\chi^2$ for addition of variable with other IHC4 and clinical variables included

	All, TTDR	N_o, TTDR
ER	3.7 P=0.055	7.2 P=0.0075
PgR	9.2 P=0.0024	1.6 p=0.21
HER2	5.8 P=0.016	8.3 P=0.0040
Ki-67	5.7 P=0.017	5.9 P=0.015

Predicted 9 year distant recurrence percent using clinical score and IHC4 score



Comparison of GHI-RS vs IHC4

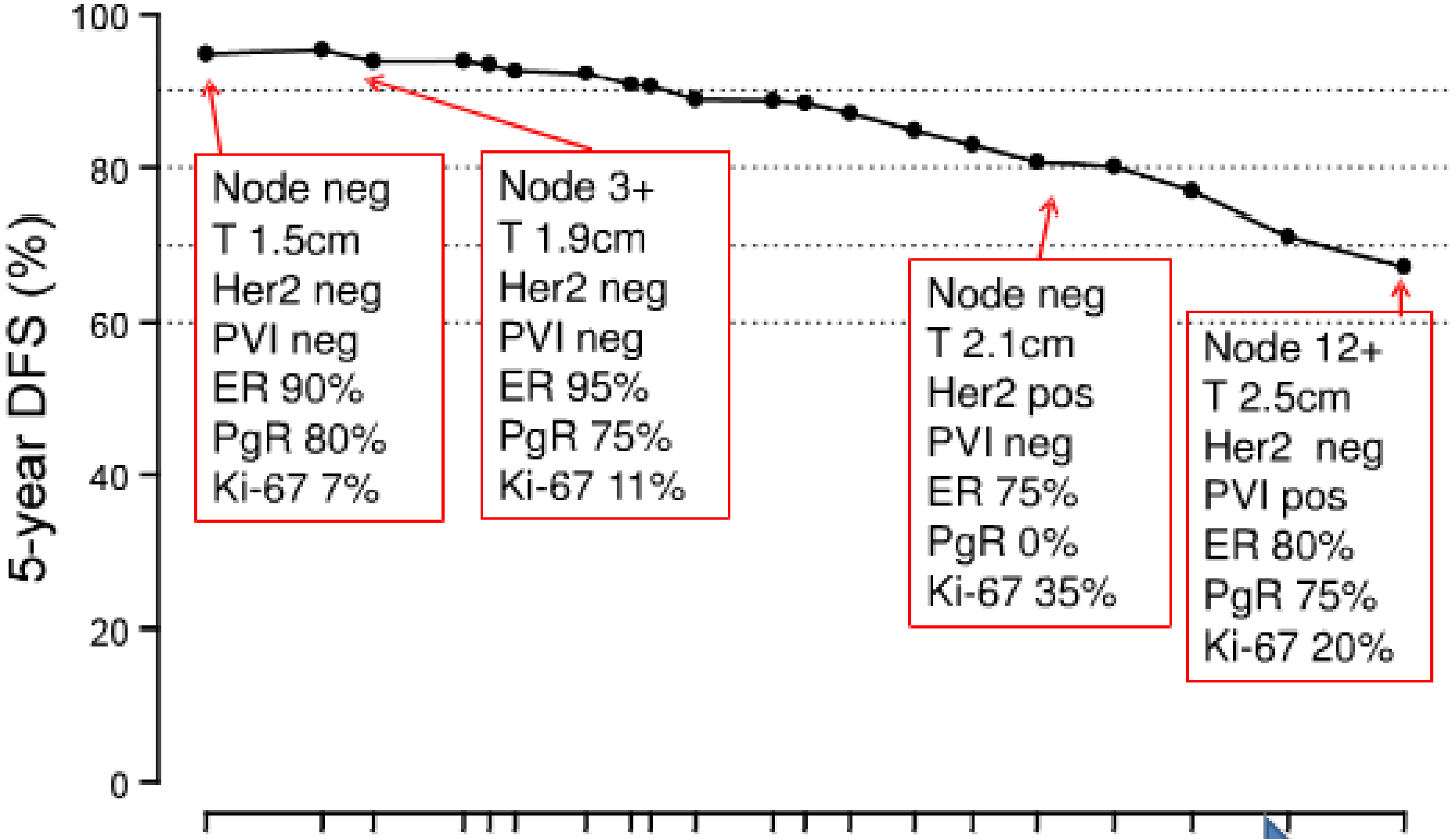
(Average $\Delta\chi^2$, Bootstrap 95% CI)

Model	All, TTDR	N_o, TTDR
Clinical (C)	111.7 (76.7-166.8)	23.3 (9.7-51.9)
C + IHC4 vs C	27.1 (9.4-55.2)	29.5 (12.6-57.8)
C + RS vs C	25.5 (9.8-46.7)	21.1 (6.7-40.8)
C +IHC4 + RS vs C	32.1 (14.9-60.3)	32.3 (16.5-61.9)
C + IHC4 +RS vs C +IHC4	4.1 (0.5-12.7)	1.7 (0.4-7.9)

Contributions to Composite Risk

Points:	0	~0.25	~0.5	~0.75	~1.5
Lymph nodes	0		1-3	4-9	10+
ER %	50+	30-49	<30%		
PgR %	20+	<20			
Ki-67 %	<14	14-33	34+		
HER2	Neg	Pos			
PVI	No	Yes			
Grade	1	2	3		
T size	≤2	2.1-4.9	5+		

STEPP 5-year DFS by Composite Risk



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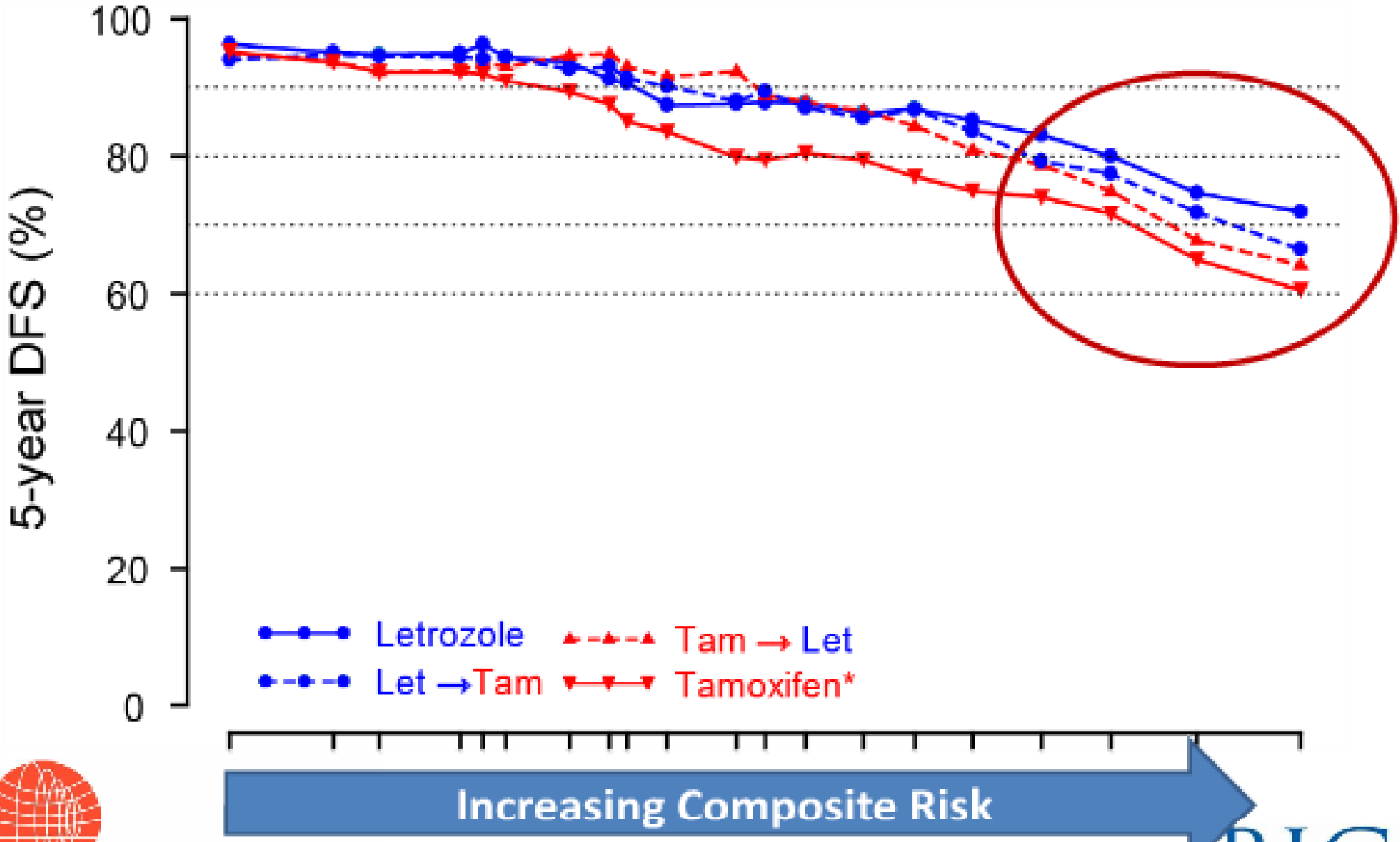
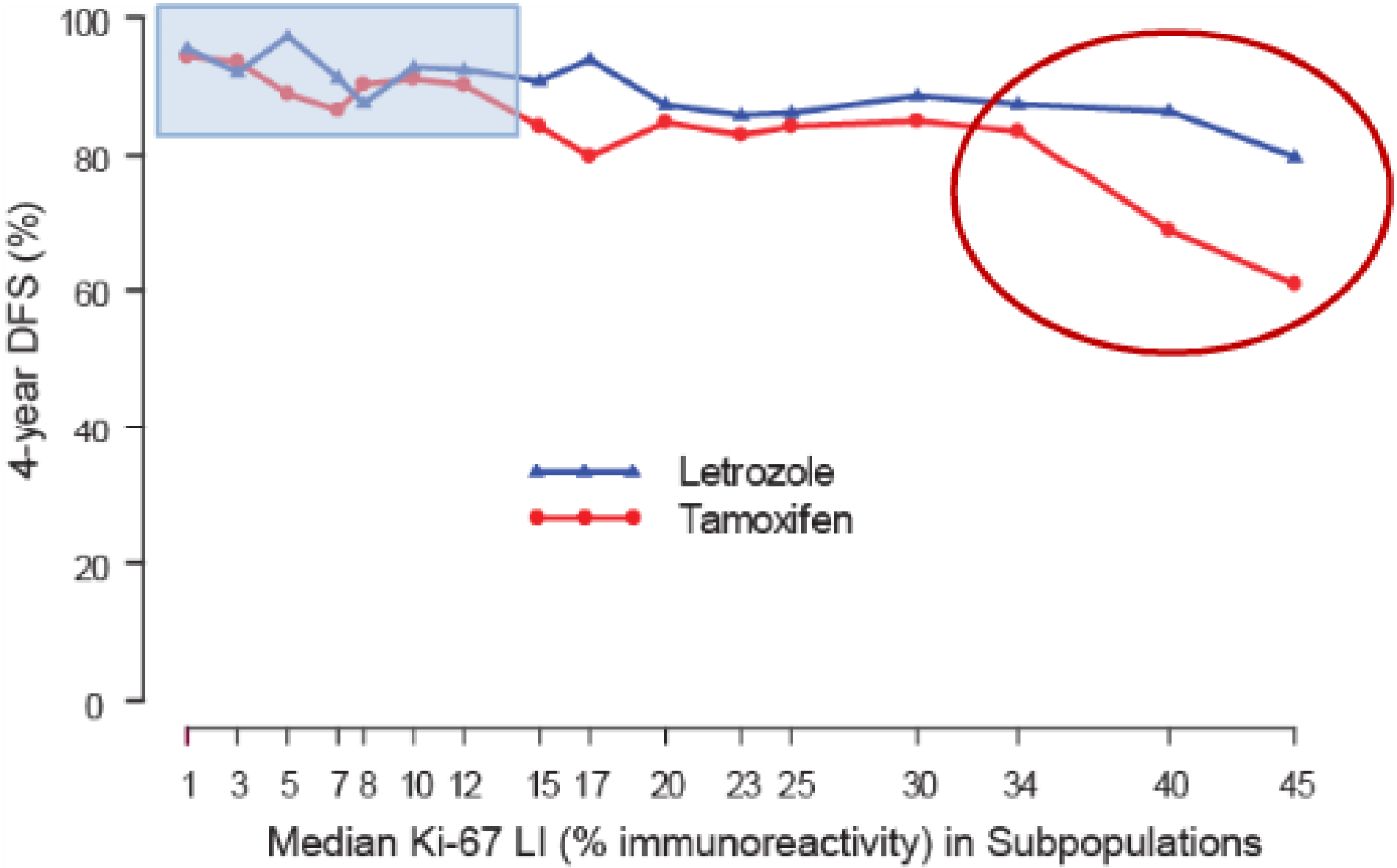


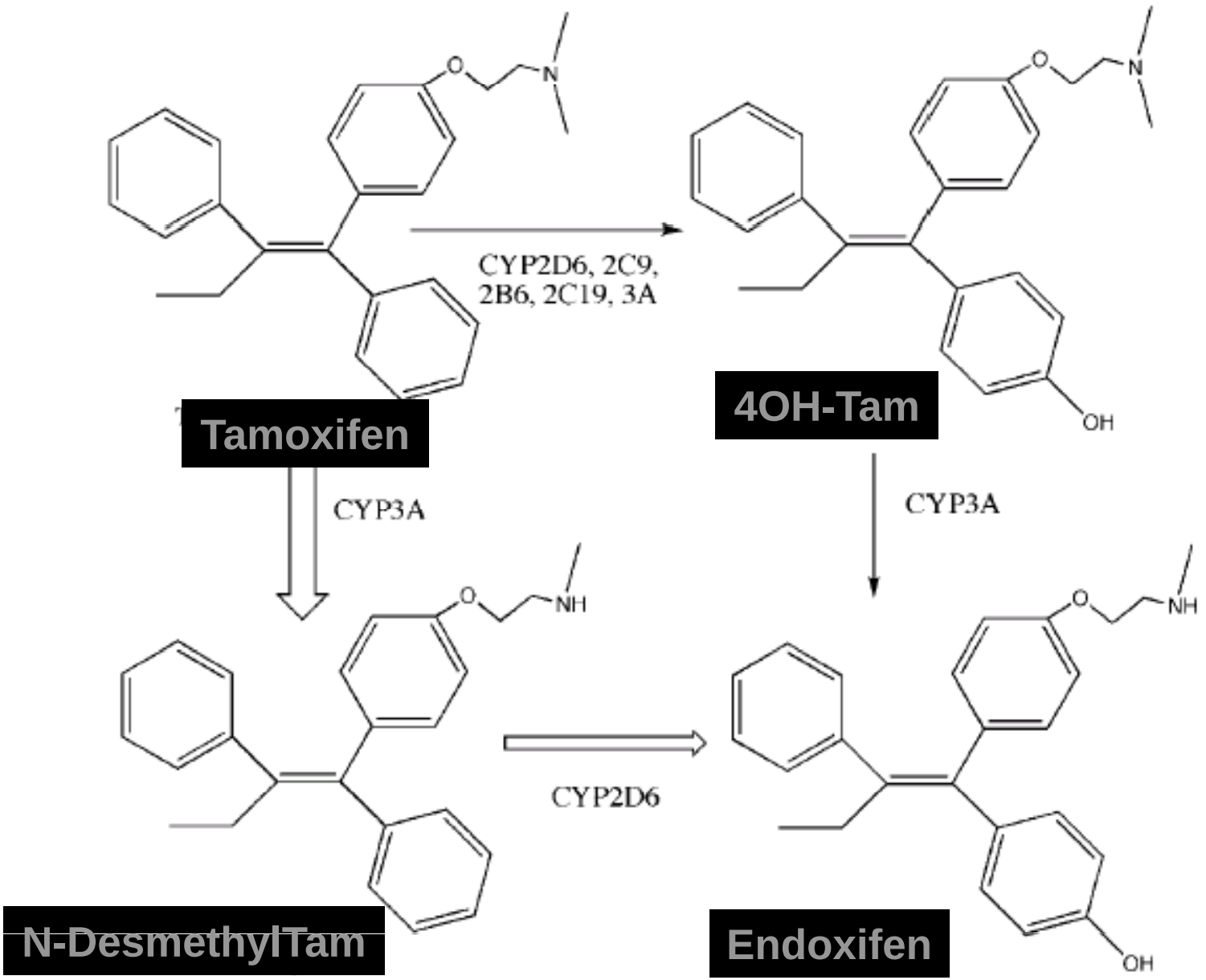
International Breast Cancer Study Group
IBCSG SABCS 2009

BIG

STEPP example: Ki-67 (SABCS 2007)



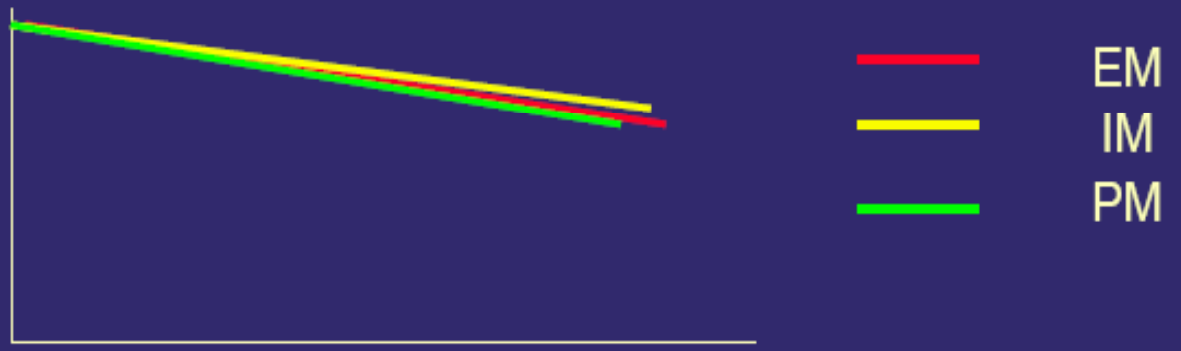
Tamoxifen - Metabolisierung



Beverage et al., J. of Pharma. Science 2007

Adjuvant Tamoxifen and CYP2D6
Goetz et al Abs#33

- World wide retrospective analysis
- 2880 pts included for genotyping (out of 4800 planned)



- NSD for invasive ductal ca
- Couldn't collect anti-depressant medication data

Conclusions(1)

- Composite scores of standard markers ER, PgR, HER2, and Ki67 could become important
- Quantitative levels of ER, PgR, Ki67 would be needed with agreed validated cut-offs
- Standardised assays with tight Quality Assurance in accredited reference labs will be crucial

Conclusions (2)

- Will we really use these scores to choose an AI or tamoxifen??
- The crucial need is to establish which scores are not only prognostic but predict for chemotherapy benefit.
- Will IHC4 etc replace GHI-RS etc? Are we heading for another USA v Rest of the World approach to planning treatment?
- Oncotype DX, Mammaprint etc will have other gene expression index competitors eg H:I, MGI continuous risk model