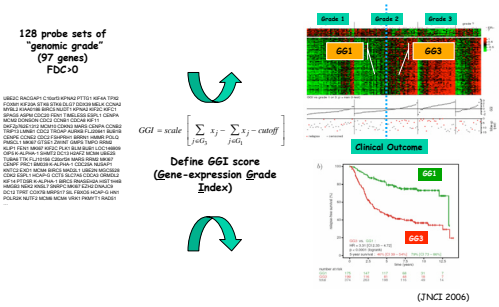
Comprehensive analysis integrating both clinico-pathological and gene expression data in more than 1500 samples: Proliferation captured by gene expression grade index appears to be the strongest prognostic factor in breast cancer

Desmedt C, Haibe-Kains B and Sotiriou C

Introduction

·Prognosis of breast cancer has been extensively studied using several clinico-pathological parameters and tumor markers reflecting different stages of disease and breast tumor biology

·Although the development of high-throughput gene expression technologies has allowed the identification of several "molecular signatures" predicting clinical outcome, no attempt has been made yet to perform a comprehensive analysis integrating both clinico-pathological and gene expression data



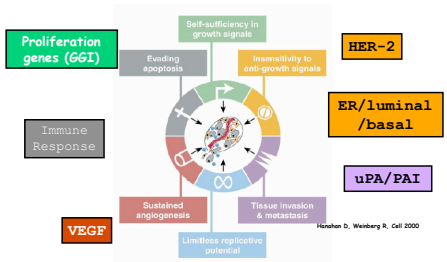
(JNCI 2006)

Aims

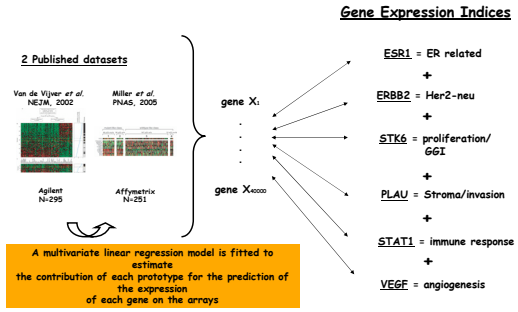
·To confirm our results in larger datasets

·To define additional gene expression indices related to breast cancer biology

·To elucidate the relationship between traditional clinico-pathological markers, gene expression patterns and their interaction with prognosis



Patients & methods



$$INDEX = \sum_{j \in P} x_j - \sum_{j \in N} x_j$$

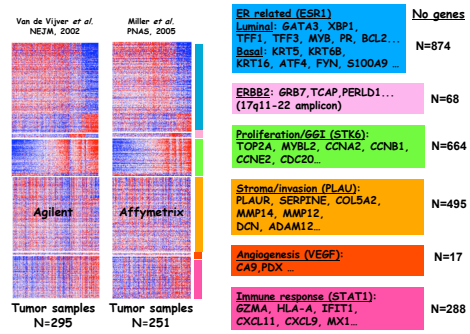
Each gene expression index is defined by the difference of the sums of the positively and negatively correlated genes for the chosen prototype

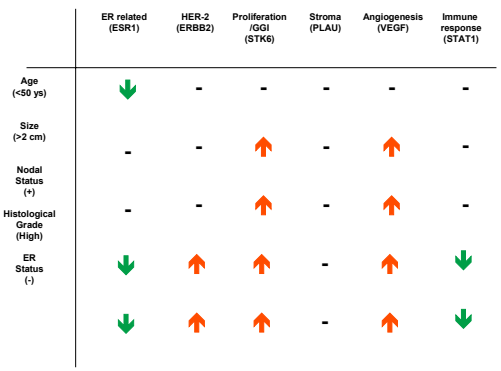
Mapped and computed on SEVERAL published microarray datasets
(Sorlie et al. PNAS 2003; Sotiriou et al PNAS 2003; van De Vijver NEJM 2002; Wang et al The Lancet 2005; Foekens et al JCO 2006; Miller et al PNAS 2005; Sotiriou et al JNCI 2006; Buyse et al JNCI in press; N=8)

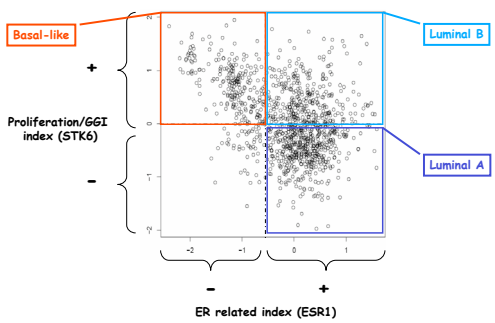
N ~ 1500 tumor samples

Results

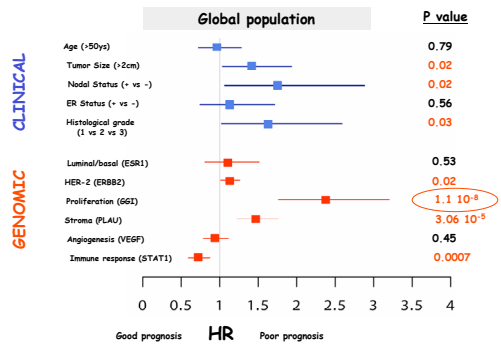
Description

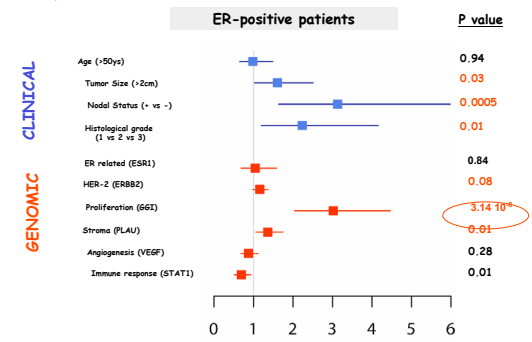


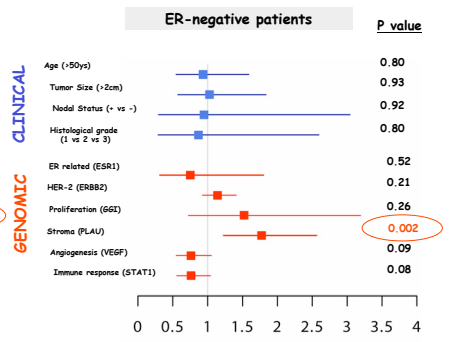




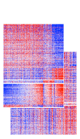
Clinical relevance





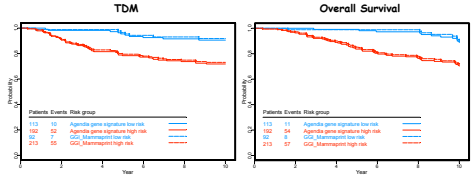


Other gene signatures

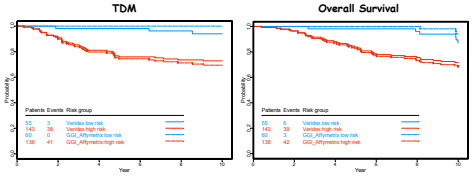


Microarray Indices	Amsterdam No (%) 70 genes (Van de Vijver et al. NEJM, 2002)	Rotterdam No (%) 76 genes (Wang et al. The Lancet, 2005)
ESR1 = luminal/basal	44 (63)	23 (30)
ERBB2 = Her2-neu	12 (17)	8 (10)
STK6 = proliferation/GGI	33 (47)	34 (44)
PLAU = stroma/invasion	13 (18)	6 (7)
STAT1 = immune response	6 (8)	9 (11)
VEGF = angiogenesis	10 (14)	6 (7)
NA = undetermined	3 (4)	23 (30)

TRANSBIG VALIDATION SERIES
Using MammaPrint® (AGENDIA)
70-gene (AMSTERDAM) versus Proliferation (GGI)



TRANSBIG VALIDATION SERIES
Using Affymetrix® (VERIDEX)
76-gene (ROTTERDAM) versus Proliferation (GGI)"



Conclusions

1. ESR1 and ERBB2 indices seem to be the most prominent discriminators dichotomizing breast tumors into two main subsets in agreement with previously proposed breast cancer subtypes
2. Almost all ER-negative and ERBB2-positive tumors were associated with high proliferation index scores
3. In contrast, ER-positive tumors showed a whole range of proliferation index values
4. Proliferation captured by the gene expression grade index (GGI) appears to be a key biological factor in breast cancer and one of the most significant indicators predicting clinical outcome far beyond ER
5. Proliferation genes seem to be an important component of many existing prognostic gene signatures. Their weight seems to be far more important in ER-positive disease
6. Tumor size and nodal status retain prognostic value in addition to proliferation