3016 - Definition of Clinically Distinct Subtypes Within Estrogen Receptor Positive Luminal Breast Carcinomas

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Background

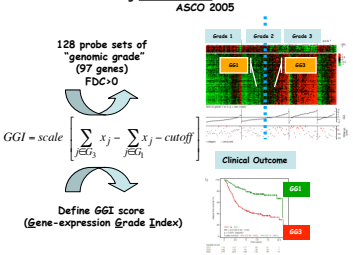
·Several microarray studies have shown that breast tumours can be grouped in at least 4 to 5 individual subtypes namely basal-like, erbB2-like and luminal-like A, B, C or 1, 2, 3.

·However, 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.

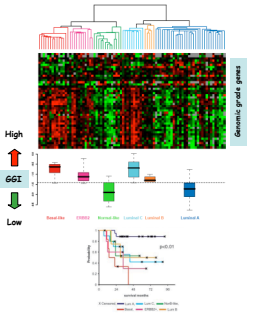
·Refinement of their molecular definition is therefore needed.

Material and Methods

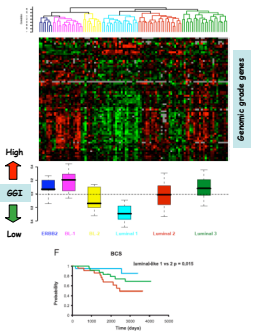
Defining Genomic Grade in Breast Carcinoma
ASCO 2005



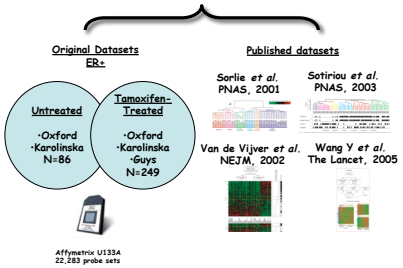
Applying Genomic Grade to Molecular Subtypes
Sorlie *et al.* PNAS 2001



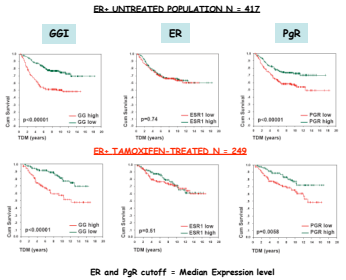
Applying Genomic Grade to Molecular Subtypes
Sotiriou *et al.* PNAS 2003



Total Number ER+/luminal subtypes = 787 samples

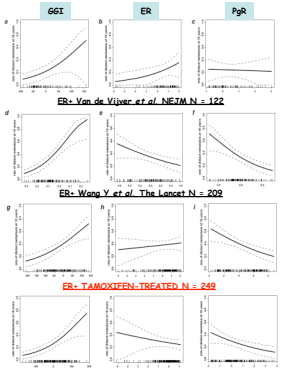


Time to Distant Metastases
GG, ER and PgR expression levels



ER and PgR cutoff = Median Expression level

Expected rate of Developing Distant Metastases at 10 Years



Systemically Untreated N = 417

	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95%CI)	p¶	Hazard ratio (95%CI)	p¶
Age (years) ≤ 50 vs >50	1.055 (0.556-2.004)	0.869	0.906 (0.416-1.975)	0.8040
Size >2cm vs ≤ 2cm	2.694 (1.618-4.485)	**0.0001**	2.153 (1.235-3.755)	**0.0068**
Histological grade 1 vs 2 vs 3	2.102 (1.461-3.024)	**0.00006**	1.446 (0.963-2.171)	0.0754
Estrogen Receptor Rich vs Poor	0.937 (0.671-1.307)	0.937	1.212 (0.667-2.202)	0.5275
Progesterone Receptor Rich vs Poor	0.536 (0.381-0.754)	**0.00034**	0.755 (0.430-1.328)	0.3300
Genomic Grade High vs Low	2.610 (1.833-3.717)	**0.0000001**	2.302 (1.241-4.271)	**0.0081**

* Only patients with complete information in all variables were included in the multivariate analysis (N=208)
¶ Based on Cox regression, stratified according to the datasets

TAMOXIFEN-TREATED N = 249

	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95%CI)	p¶	Hazard ratio (95%CI)	p¶
Age (years) ≤ 50 vs >50	0.926 (0.328-2.612)	0.8840	0.807 (0.223-2.916)	0.7440
Size >2cm vs ≤ 2cm	2.002 (1.157-3.463)	**0.0130**	1.712 (0.897-3.268)	0.1030
Histological grade 1 vs 2 vs 3	1.728 (1.128-2.647)	**0.0120**	1.071 (0.624-1.839)	0.8040
Nodal status Positive vs Negative	1.444 (0.836-2.493)	0.1870	1.053 (0.554-2.001)	0.8760
Estrogen Receptor Rich vs Poor	0.839 (0.512-1.376)	0.4860	0.982 (0.547-1.764)	0.9530
Progesterone Receptor Rich vs Poor	0.485 (0.291-0.806)	**0.0050**	0.751 (0.409-1.381)	0.3570
Genomic Grade High vs Low	3.119 (1.861-5.228)	**<0.000001**	2.147 (1.042-4.422)	**0.0380**

* Only patients with complete information in all variables were included in the multivariate analysis
¶ Based on Cox regression, stratified according to the datasets

Conclusions

·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.

·These subtypes may provide important stratification for future breast cancer trials investigating the effect of treatment on ER+ breast cancers and hence potential to improve breast cancer management.

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