COMPARISON OF MAMMAPRINT AND TARGETPRINT RESULTS WITH CLINICAL PARAMETERS IN GERMAN PATIENTS (PATH) WITH EARLY STAGE BREAST CANCER

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mammaprint™
decoding breast cancer.

PATH Patients Tumorbank of Hope

Background

Currently, for breast cancer patients, adjuvant treatment decision-making is based on risk assessments using clinicopathological criteria. However, patients with similar tumor characteristics can have strikingly different disease outcomes, reflecting the heterogeneity of breast cancer. Therefore, risk assessment by clinicopathological criteria allocates patients to adjuvant systemic therapy resulting in both under- and overtreatment. The 70-gene signature MammaPrint has been developed to improve the prediction of disease outcome and thereby improve the allocation of adjuvant systemic therapy (1-3). Subsequent validation studies have shown MammaPrint™ can accurately identify breast cancer patients who have a good prognosis of developing distant metastases and therefore would safely be spared chemotherapy (4-7).
This study was set up to determine the validation of MammaPrint in a German patient population, using samples from a unique tumorbank the 'Patients Tumor bank of Hope' (PATH), initiated by the breast cancer initiative Mamazone – women and genomics against breast cancer, set up to enable patients to donate tissue for research purposes.

Goals

The 70-gene tumor expression profile "MammaPrint" was established as a powerful predictor of disease outcome in breast cancer patients. Also, a microarray based test called TargetPrint was developed as a quantitative assessment of the mRNA expression level of ER, PR and HER2. This study was performed as a validation of MammaPrint and TargetPrint in a German breast cancer population from 'Patients Tumor bank of Hope' (PATH), a German tumor bank, initiated by the breast cancer initiative Mamazone – women and genomics against breast cancer.

Methods

Frozen tumor samples were collected by 'Patients Tumor bank of Hope' (PATH), the German tumor bank. Patients were diagnosed with breast cancer stage I and II between November 2005 and April 2008 in Breast Centers in Germany. Frozen tumor samples from 140 patients were classified as being either good or poor prognosis signature by MammaPrint (at low or high risk for developing distant metastasis) and compared to actual adjuvant treatment management, the St Gallen guidelines and Adjuvant!Online. Next, we compared IHC and fluorescent in situ hybridization (FISH) assessments of ER, PR and HER2 with gene expression readouts using TargetPrint.

Overview of patients

	MammaPrint good prognosis 78 patients (56%)	MammaPrint poor prognosis 62 patients (44%)	total
Age, years			
< 36	1	1	2
36-45	11	5	16
46-55	17	12	29
>55	49	44	93
Histology			
Ductal	59	49	108
Lobular	12	11	23
Other	7	2	9
Grade			
Good	11	3	14
Intermediate	58	30	88
Poor	9	29	38
Stage			
I	35	15	50
IIa	27	29	56
IIb	15	17	32
IIIa	0	1	1
IIIb	1	0	1
Size			
<1/=1 cm	4	3	7
>1- </=2 cm	39	18	57
>2 </= 5 cm	34	38	72
> 5 cm	1	3	4
LN			
Negative	54	40	94
Positive	24	22	46
ER positive	77	39	116
ER negative	1	23	24
PR positive	68	30	98
PR negative	10	32	42
Her2 positive	3	6	9
Her2 negative	74	55	129
Her2 unknown	1	1	2

Treatment advice

	actual treatment	MammaPrint poor prognosis	MammaPrint good prognosis	St Gallen high risk	St Gallen intermediate	St Gallen low risk	Adjuvant high risk	Adjuvant low risk
no treatment	2	0	2	0	2	0	1	1
ET	59	19	40	1	52	6	28	31
CT	23	19	4	7	16	0	22	1
CT plus ET	52	21	31	0	51	1	40	12
unknown	4	3	1	2	2	0	4	0
total	140	62	78	10	123	7	95	45

Considering patients with known treatment advice: Of 59 MammaPrint poor prognosis patients, 19 did not receive chemotherapy and are potentially undertreated; whereas 35 out of 77 good signature prognosis patients received chemotherapy and are potentially over treated. Concordance between risk assessment and treatment advice may seem largest with St Gallen, for who the majority is intermediate risk.

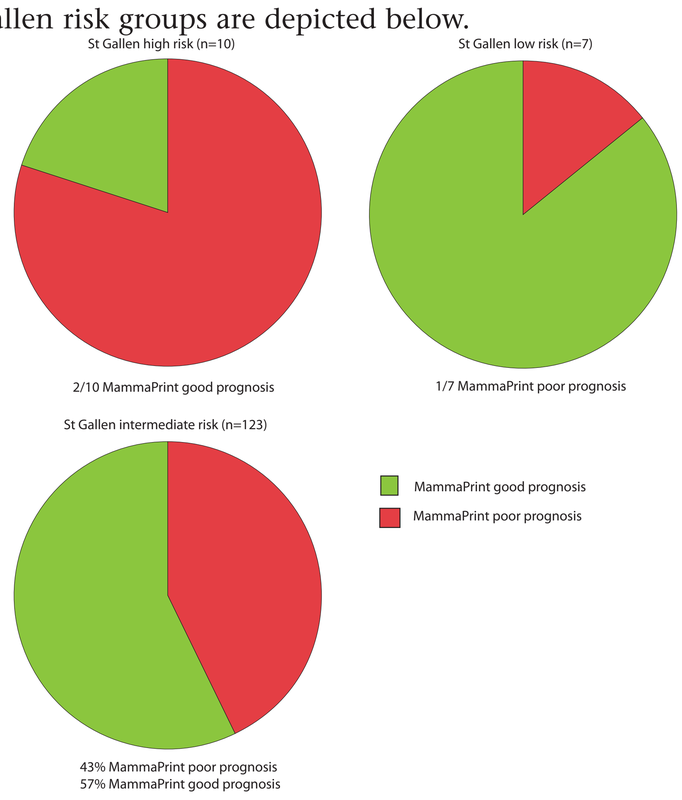
Results

A total of 170 samples were collected from the German tumor bank, of which 26 samples were ineligible for gene expression profiling given that they contained no or too little tumor cells. In the remaining 144 samples, 4 had insufficient RNA quality and 140 (97%) could successfully be hybridized. The median age of these 140 patients was 62.5 years.
Among the 140 patients, 78 (56%) were classified as good prognosis, whereas 62 (44%) were classified as poor prognosis. Patients demographics and therapy information was available through PATH, see tables 'overview of patients' and 'treatment advice'.

Concordance of risk assesssment

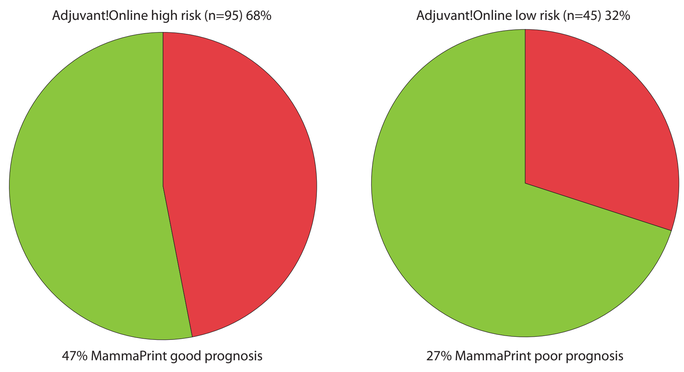
St Gallen

The majority of patients is classified as intermediate risk by St Gallen. MammaPrint profiles for the St Gallen risk groups are depicted below.



Adjuvant!Online

When comparing MammaPrint results with risk classification by Adjuvant!Online - as described by Buyse et al.[4]- there is discordancy in 41% of patients.



Microarray based receptor read-out

Roepman et al.[8] recently showed microarray read-out of hormone and HER2 receptor status to be strongly correlated with IHC assessment, especially for ER and HER2. Comparison of microarray receptor results with IHC/FISH performed at the local hospitals in Germany indicated highly similar results with a concordance of 97% for ER; 86% for PR; and 94% for HER2. 2 samples that were IHC 2+ and not scored by FISH, were both classified as negative by TP.

Microarray TargetPrint	PATH	IHC		
	ER	pos	neg	total
	pos	114	2	116
	neg	2	22	24
	PR	pos	neg	total
	pos	86	12	98
	neg	8	34	42
	Her2	pos	neg	total
	pos	7	2	9
	neg	6	123	129

Conclusion

MammaPrint has been validated in multiple studies and has been shown to provide improved prediction of recurrence risk than currently used guidelines. Here we show feasibility of MammaPrint in a German study population. MammaPrint would have resulted in altered treatment advice in ~40% of patients. TargetPrint shows high concordance for hormone receptors and Her2 with IHC.

References

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(5) Bueno-de-Mesquita et al. Lancet Oncol 2007
(6) Wittner et al. Clin Can Res 2008
(7) Mook et al. Breast Can Res Treat 2008
(8) Roepman et al. abstract San Antonio 2008

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