Clinical Utility of Multigene Assay in Breast Cancer

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Disclosure Statement

- I have **no** relevant financial or nonfinancial relationships in the products or services described, reviewed, evaluated or compared in this presentation.

- I have **no** actual or potential conflict of interest in relation to this presentation.

The American Journal of Surgery (2012) 203, 751–758

The role of the breast cancer surgeon in personalized cancer care: clinical utility of the 21-gene assay

Christine Laronga, M.D.[a,*], Jay K. Harness, M.D.[b], Matthew Dixon, M.D.[c], Patrick I. Borgen, M.D.[c]

CONCLUSIONS: The advent of genomic analysis has advanced the treatment and management of breast cancer toward the goal of personalized care. Therefore, the role of the surgeon now extends beyond extirpation of the tumor and includes an understanding of the biology of the disease as well as an appreciation of this new technology. Breast cancer surgeons should seize this opportunity to provide patients and colleagues with this information in an expeditious manner to optimize clinical outcomes.

Implementation of Surgeon-Initiated Gene Expression Profile Testing (Oncotype DX) Among Patients With Early-Stage Breast Cancer to Reduce Delays in Chemotherapy Initiation.

CONCLUSION:
Developing consensus on Oncotype DX testing criteria and implementing streamlined workflows has led to clinically significant reductions in wait times to chemotherapy decision making and initiation.

Losk K et al. J Oncol Pract. **2017** Sep;**13**(9):e815-e820

Multigene assay(MGA) in breast cancer

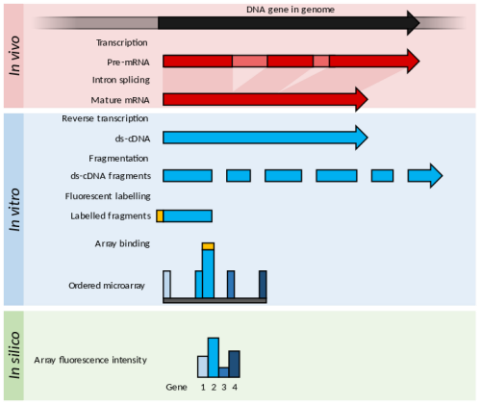
- **Historical overview of MGA**
- **Clinical utility of MGA as a biomarker**
  - **Prediction of prognosis**
  - **Prediction of treatment response**
- **Summary & Conclusion**

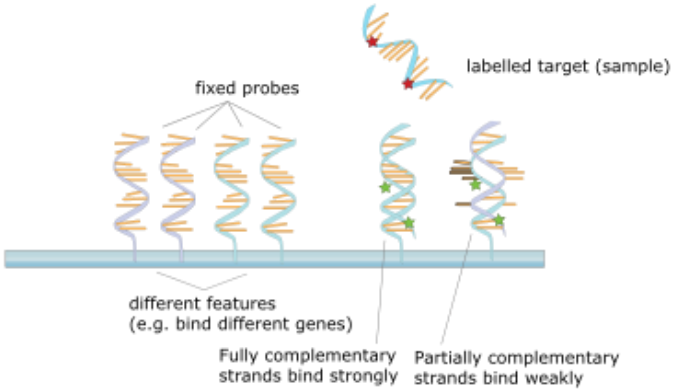
Overview of Multigene Assay

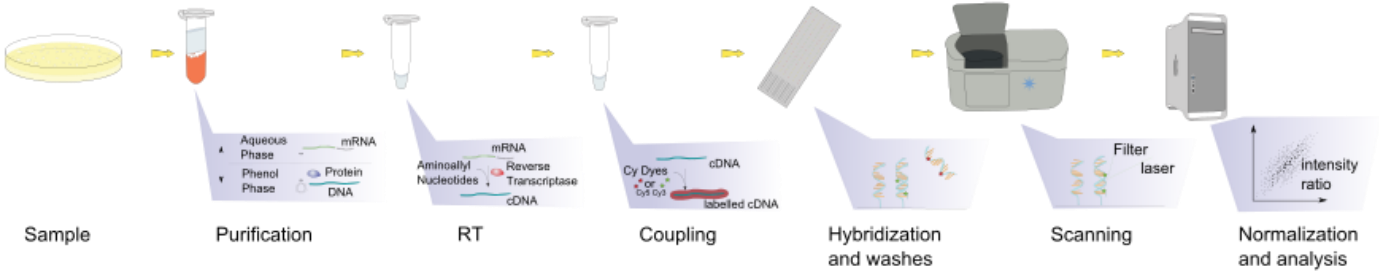
Gene Expression Profiling & Multigene Assay(MGA)

Gene expression profiling

- In 1995, serial analysis of gene expression (SAGE) + Microarray → cDNA Microarray → gene expression profiling

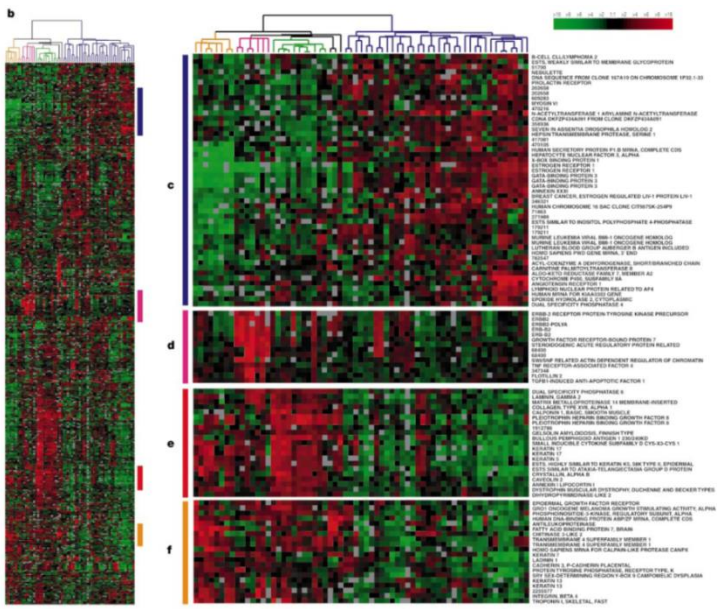






Intrinsic subtypes & Risk prediction

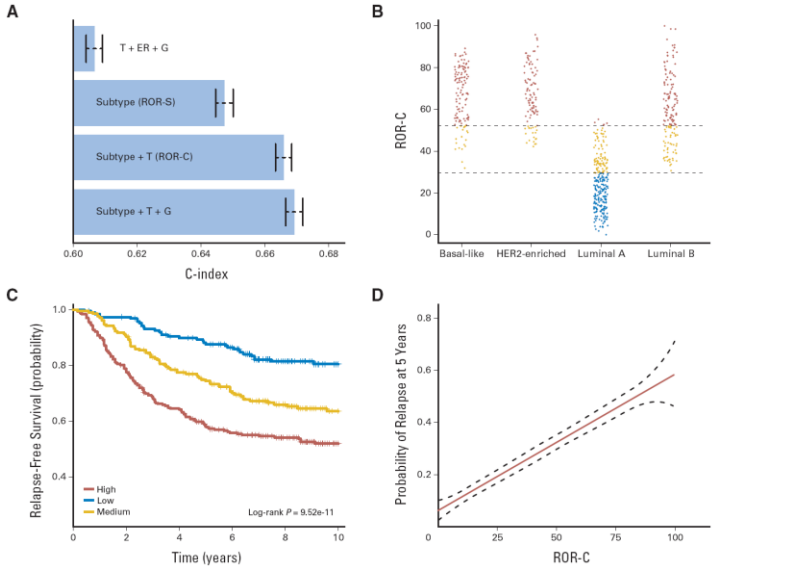
- In 2000, **intrinsic subtypes** of breast cancer



Nature. 2000 Aug 17;406(6797):747-52.

$$\text{ROR-S} = 0.05 \cdot \text{basal} + 0.12 \cdot \text{HER2} + \\ -0.34 \cdot \text{LumA} + 0.23 \cdot \text{LumB} \quad (1)$$

$$\text{ROR-C} = 0.05 \cdot \text{basal} + 0.11 \cdot \text{HER2} + \\ -0.23 \cdot \text{LumA} + 0.09 \cdot \text{LumB} + 0.17 \cdot \text{T} \quad (2)$$

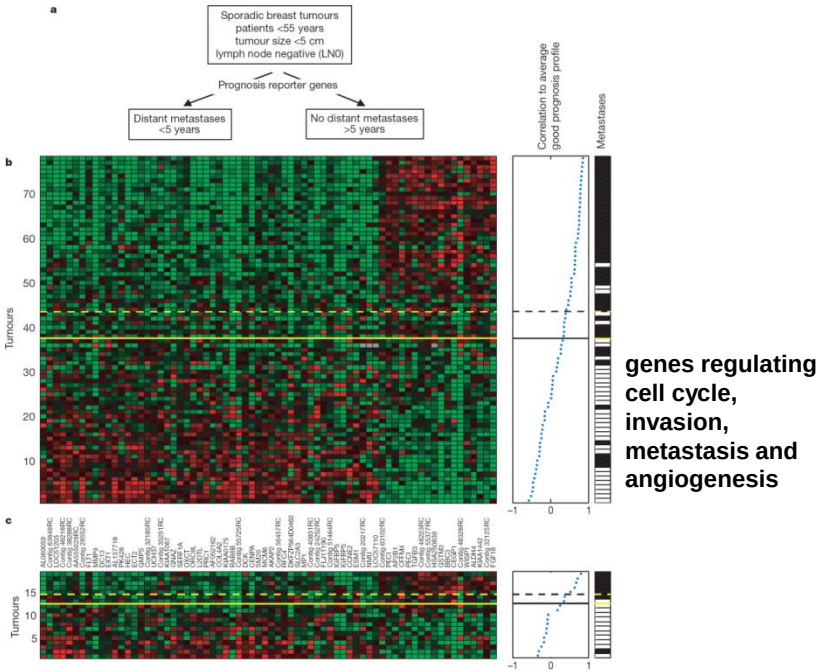


- In 2009, risk prediction with **P**rediction **A**nalysis of **M**icroarray **of 50** gene set(**PAM50; Prosigna®**) ; ROR-S, ROR-C

J Clin Oncol 27:1160-1167. © 2009

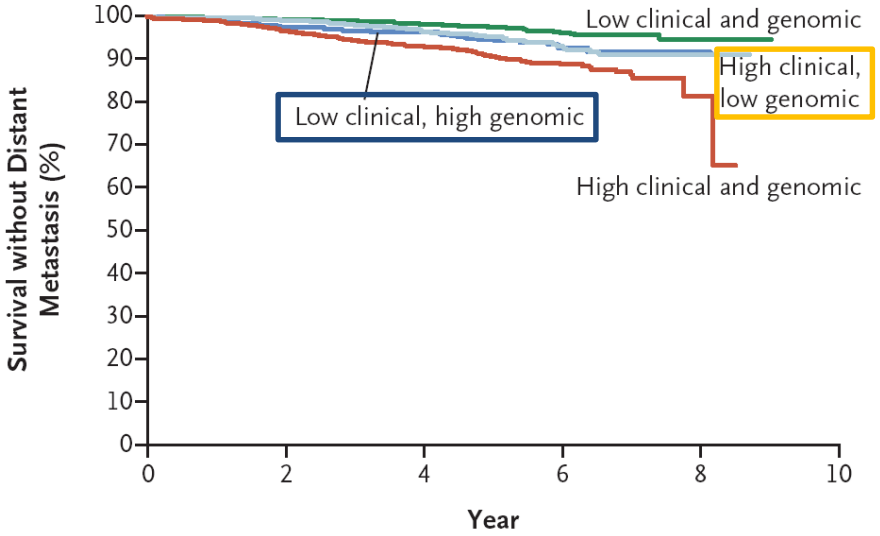
Clinical application & Phase III RCT

- In 2002, prediction of outcome with 70-gene assay (**MammaPrint®)**



genes regulating cell cycle, invasion, metastasis and angiogenesis

Nature. 2002 Jan 31;415(6871):530-6.

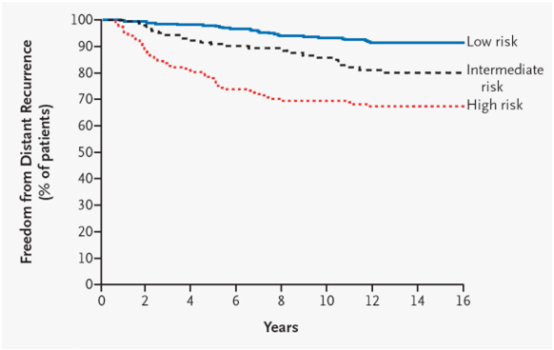


- In 2016, the first phase III RCT (**MINDACT** trial); randomized discordant risk groups for chemotherapy

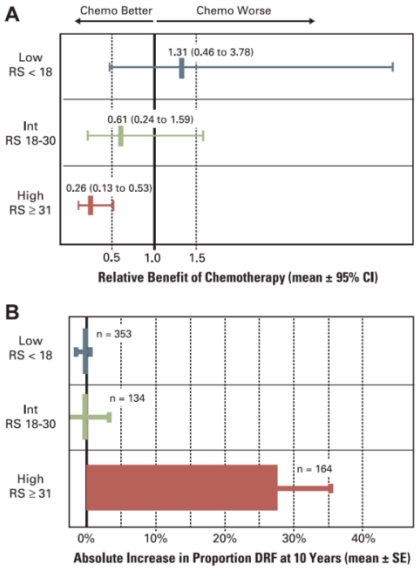
N Engl J Med 2016;375:717-29.

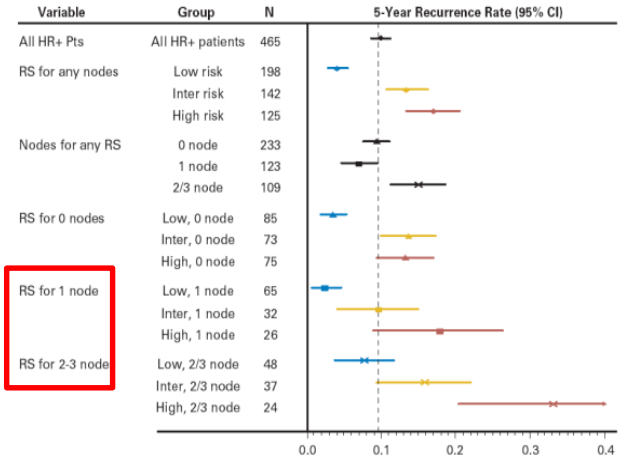
Clinical utility of 21-gene assay(OncotypeDX®)

- In 2004, recurrence in **tam-treated, node- BC** from NSABP B-14
- In 2006, benefit of chemotherapy in **node-, ER+** BC from NSABP B-20



N Engl J Med 2004;351:2817-26.



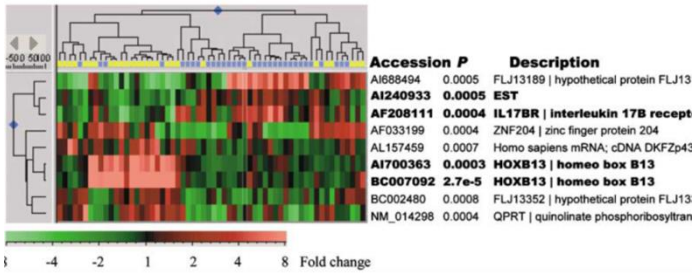


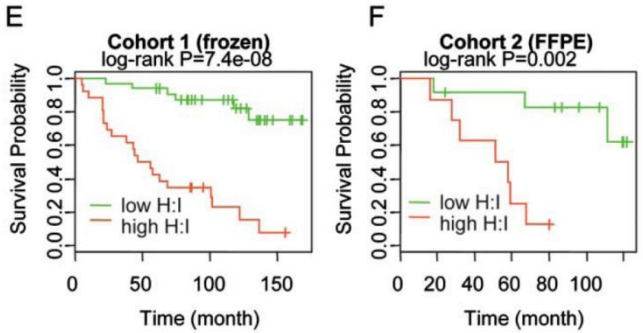
- In 2008, recurrence in **chemo-treated, HR+, node+ BC** from Intergroup E2197 trial

J Clin Oncol 24:3726-3734. © 2006 *J Clin Oncol 26:4063-4071. © 2008*

Late recurrence: 2-gene(H/I) ratio (BCI®)

- In 2004, HOXB13:IL17BR gene ratio **in tam-treated, HR+ BC**





- In 2013**,** validation of H/I ratio in patients treated **with extended therapy of letrozole** from MA.17

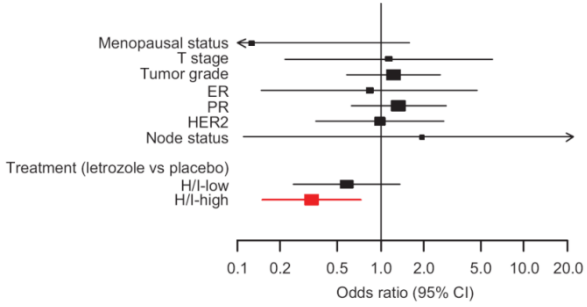


Table 4. Estimates of recurrence-free survival (RFS) at 5 years in patients who were treated with placebo or extended letrozole

	Placebo		Letrozole	
Patient subgroups	**No. of patients (%)**	**5-Year RFS (95% CI, %)**	**No. of patients (%)**	**5-Year RFS (95% CI, %)**
All patients	127 (100)	80.4 (68.0 to 88.4)	122 (100)	90.1 (82.3 to 94.6)
H/I-low	65 (51)	87.0 (76.8 to 92.9)	63 (52)	91.0 (83.1 to 95.3)
H/I-high	62 (49)	73.0 (56.6 to 84.1)	59 (48)	89.5 (80.3 to 94.5)

Cancer Cell. 2004 Jun;5(6):607-16. J Natl Cancer Inst;2013;105:1036–1042

Late recurrence: EndoPredict®

- In 2011, EP & EPclin scores were validated in **ER+, HER2- BC treated with only endocrine therapy** from ABCSG 6 & 8 trials

$$\Delta C_t(\mathrm{GOI}) = 20 - C_t(\mathrm{GOI}) + [C_t(CALM2) + C_t(OAZ1) + C_t(RPL37A)]/3 \quad (A)$$

The ΔC_t values were combined into the predictive unscaled risk score s_u.

$$s_u = 0.41 \cdot \Delta C_t(BIRC5) - 0.35 \cdot \Delta C_t(RBBP8) + 0.39 \cdot \Delta C_t(UBE2C) - 0.31 \cdot \Delta C_t(IL6ST) - 0.26 \cdot \Delta C_t(AZGP1) + 0.39 \cdot \Delta C_t(DHCR7) - 0.18 \cdot \Delta C_t(MGP) - 0.15 \cdot \Delta C_t(STC2) - 2.63 \quad (B)$$

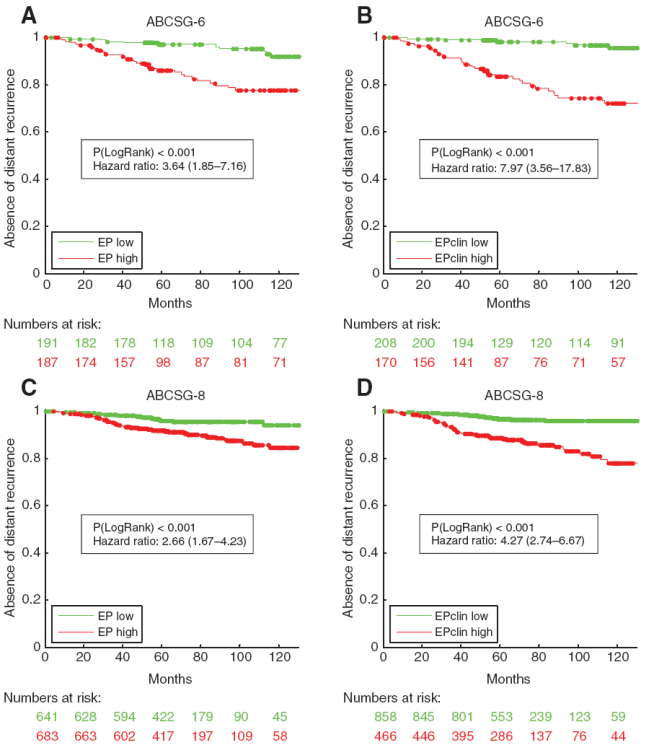
To avoid negative score values, we defined the final, rescaled EP risk score (s).

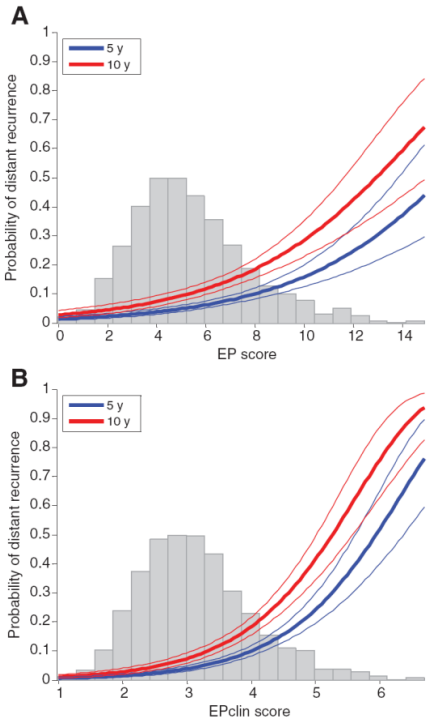
$$s = \begin{cases} 0, & \text{if } 1.5 \cdot s_u + 18.95 < 0 \\ 15, & \text{if } 1.5 \cdot s_u + 18.95 > 15 \\ 1.5 \cdot s_u + 18.95, & \text{otherwise} \end{cases} \quad (C)$$

The EP risk score ranges from 0 to 15; higher values indicate a higher risk of recurrence.

EPclin (s_{clin}), a combined score consisting of the EP risk score and clinical parameters, was constructed from the training set:

$$s_{clin} = 0.35 \cdot t + 0.64 \cdot n + 0.28 \cdot s \quad (D)$$





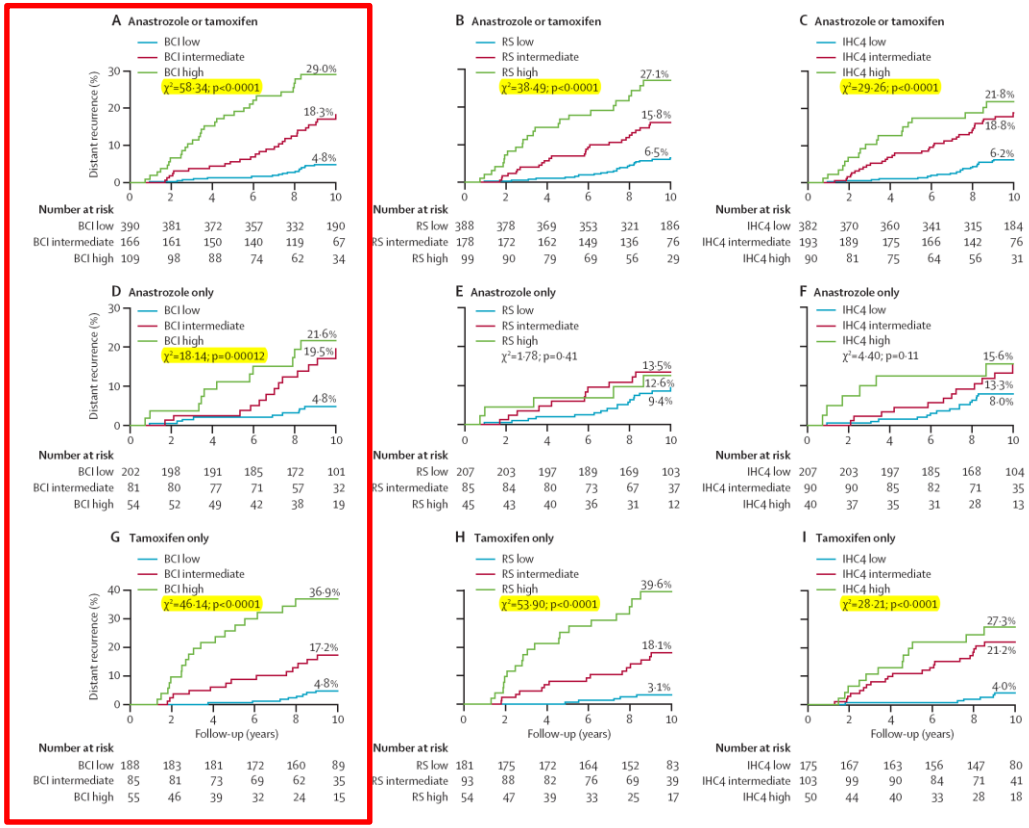
Clin Cancer Res; 17(18); 6012–20. ©2011

Summary of MGAs

	MammaPrint	OncotypeDX	Prosigna (PAM50)	BCI(Breast cancer index)	EndoPredict
Gene	70	21 (T:16+R:5)	55 (T:50+R:8)	11 (T:7+R:4)	11 (T:8+R:3)
Technique	Microarray	qRT-PCR	qRT-PCR & nCounter	qRT-PCR	qRT-PCR
Output	Risk of distant recurrence at 5 years	Recurrence Sore(RS)	Subtype & Risk of relapse (ROR) score	H/I ratio & MGI	EP & EPclin scores
Regulation	Centralized Lab	Centralized Lab	Decentralized testing	Centralized Lab	Decentralized testing
Development papulation	Age<55, node-, tam, chemo,	Pre-/post-menopause, node-,tam	Pre-/post-menopause, ER+, tam, chemo	Post-menopause ER+, tam	Post-menopause ER+,HER2-, tam
LOE	1A	1B	1B	1B	1B
Validation set	**MINDACT**	NSABP B-14, 20; Intergroup E2197	Danish cohort study	Stockholm trial, MA.17	ABCSG 6, 8
Ongoing trial	-	TAILORx RxPONDER	RxPONDER OPTIMA	-	UNIRAD

Comparing MGAs for clinical application

- A prospective comparison of the BCI, 21-gene RS, and IHC4 with tissue blocks from **TransATAC** study population
- Prediction of late distant recurrence in patients with ER+ BC



Lancet Oncol. 2013 Oct;14(11):1067-76.

Criteria of evidence for recommendations

- Analytical validity; accuracy, reliability & reproducibility
- Clinical validity; to divide population into biological or clinical different groups
- Clinical utility; to provide clinically useful information beyond clinico-pathological indicators for improved outcomes

Table 1 Categories of genetic test applications and some characteristics of how clinical validity and utility are assessed

Application of test	Clinical validity	Clinical utility
Diagnosis (symptomatic patient)	Association of marker with disorder	Improved clinical outcomes[a]—health outcomes based on diagnosis and subsequent intervention or treatment
		Availability of information useful for personal or clinical decision-making
		End of diagnostic odyssey
Disease screening (asymptomatic patient)	Association of marker with disorder	Improved health outcome based on early intervention for screen positive individuals to identify a disorder for which there is intervention or treatment, or provision of information useful for personal or clinical decision making
Risk assessment/susceptibility	Association of marker with future disorder (consider possible effect of penetrance)	Improved health outcomes based on prevention or early detection strategies
Prognosis of diagnosed disease	Association of marker with natural history benchmarks of the disorder	Improved health outcomes, or outcomes of value to patients, based on changes in patient management
Predicting treatment response or adverse events (pharmacogenomics)	Association of marker with a phenotype/metabolic state that relates to drug efficacy or adverse drug reactions	Improved health outcomes or adherence based on drug selection or dosage

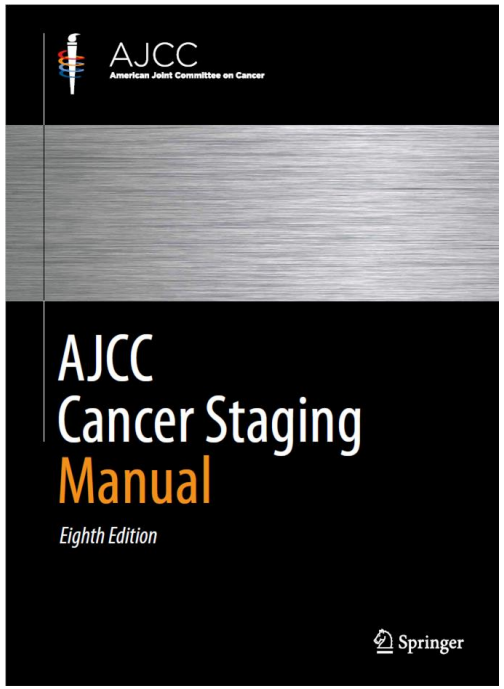
[a]Clinical outcomes are the net health benefit (benefits and harms) for the patients and/or population in which the test is used.

Genet Med 2009:11(1):3–14.

Clinical Utility of Multigene Assay

As a Prognostic Biomarker

MGA in AJCC Breast Cancer Staging



48. Breast

Genomic Profile for Pathologic Prognostic Staging

When Oncotype Dx Score is less than 11...

And TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	Then the Pathological Prognostic Stage Group is...
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes

1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.

2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1-2 N0 M0 HER2–negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.

3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score <11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

MGA for prediction of prognosis: EGTM guidelines

- All appear to provide prognostic information for relapse-free survival independent of the traditional prognostic factors such as tumour size, tumour grade and lymph node status.
- The majority were discovered and validated in ER-positive, HER2-negative, lymph node–negative patients between 40 and 65 years of age. Oncotype DX, MammaPrint, Endo-Predict and Prosigna (see below), however, were also found to be prognostic in lymph node–positive patients (1–3 metastatic nodes), see below.

European Journal of Cancer 75 (2017) 284–298

Clinical Utility of Multigene Assay

As a Predictive Biomarker

Clinical Utility of Multigene Assay As a Predictive Biomarker(1)

For Decision Making on Adjuvant Chemotherapy of Breast Cancer

ASCO Recommendations for MGA on adjuvant chemotherapy; focused update

		OncotypeDX	EndoPredict	PAM50	BCI	MammaPrint
ER/PgR(+) HER2(-)	Node (-)	**may be used**	**may be used**	**may be used**	**may be used**	**may be used in high clinical risk**
		evidence, **high, strong**	evidence, intermediate, moderate	evidence, **high, strong**	evidence, intermediate, moderate	evidence, **high**, **Strong**
	Node (+)	**should not**	**should not**	**should not**	**should not**	**may be used in N1, high clinical risk**
		evidence, intermediate, strong	evidence, insufficient, moderate	evidence, intermediate, moderate	consensus, insufficient, strong	evidence, **high**, moderate
HER2(+)		**should not**	**should not**	**should not**	**should not**	**should not**
		consensus, insufficient, strong	consensus, insufficient, strong	consensus, insufficient, strong	consensus, insufficient, strong	consensus, low, Moderate
TN		**should not**	**should not**	**should not**	**should not**	**should not**
		consensus, insufficient, strong	consensus, insufficient, strong	consensus, insufficient, strong	consensus, insufficient, strong	consensus, insufficient, strong

J Clin Oncol. 2017 Aug 20;35(24):2838-2847.

Clinical use of MGA on adjuvant therapy of breast cancer: Updated guidelines from EGTM

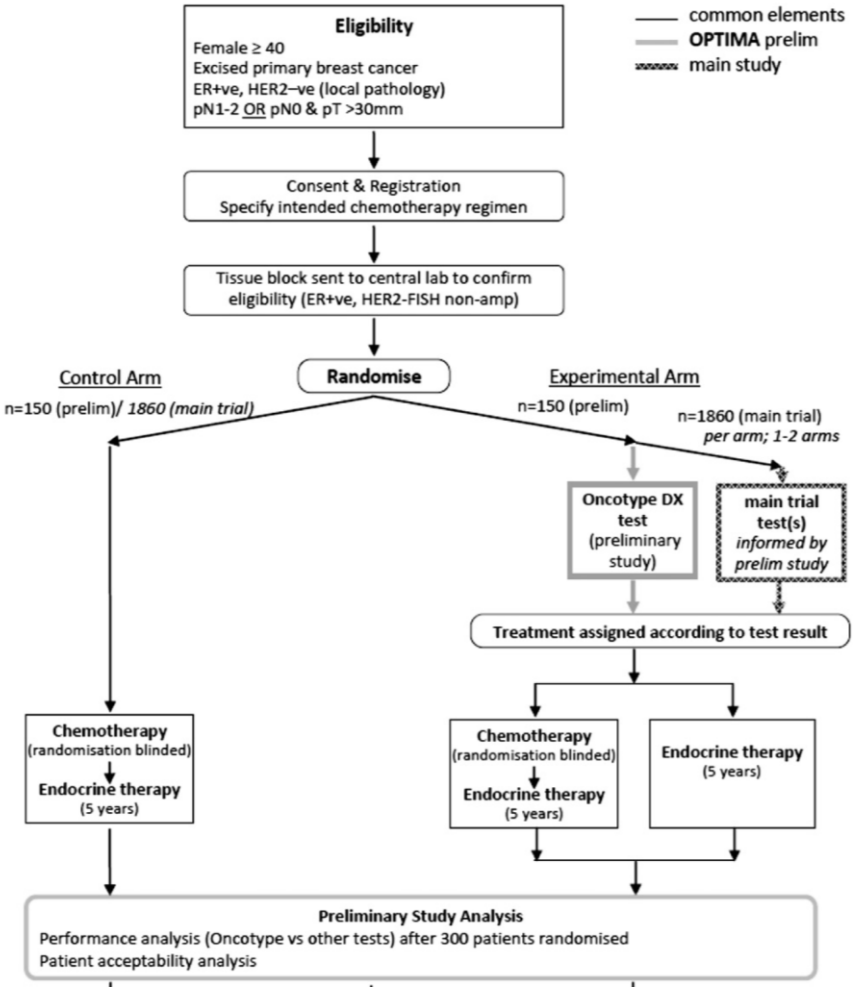
		OncotypeDX	EndoPredict	PAM50	BCI	MammaPrint
ER/PgR(+) HER2(-)	Node (-)	**may be used**	**may be used**	**may be used**	**may be used**	**may be used**
		LOB: IB SOR: A	LOB: IB SOR: A	LOB: IB SOR: A	LOB: IB SOR: A	LOE:IA SOR:A
	Node (+)	**may be used in N1**	**May be used in N1**	**May be used in N1**	**should not**	**may be used in N1**
		LOB:IB SOR:A	LOB: IB SOR: A	LOB: IB SOR: A	LOB: IB SOR: A	LOB:IA SOR:A

Eur J Cancer. 2017 Apr;75:284-298.

Differences in recommendations of MGA on adjuvant chemotherapy

	ASCO	NCCN	ESMO	St. Gallen	EGTM
Oncotype DX	LN-	LN-,LN+	LN-,LN+	LN-,LN+	LN-,LN+
EndoPredict	LN-	-	LN-,LN+	LN-,LN+	LN-,LN+
PAM 50	LN-	-	LN-,LN+	LN-,LN+	LN-,LN+
BCI	LN-	-	-	LN-,LN+	LN-
MammaPrint	LN-,LN+	-	LN-,LN+	LN-,LN+	LN-,LN+

Optimal Personalized Treatment of early breast cancer usIng Multi-parameter Analysis (OPTIMA) Trial in UK; Selecting BC Patients for Chemotherapy



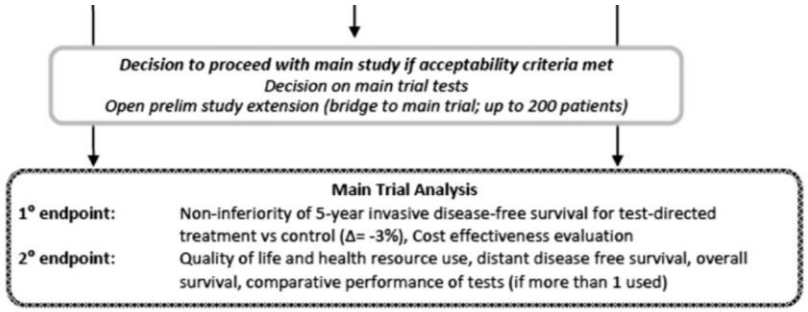


Fig 1. The design of the OPTIMA trial.

Gene-based Assays	Perou and Sorlie (academic) Oncotype DX (Genomic Health Inc.) MammaPrint (Agendia) Rotterdam signature (Academic) PAM50 (ARUP Laboratories & nanoString Technologies) Breast Cancer Index (bioTheranostics) Blueprint (Agendia) MAPQUANT-Dx Genomic Grade (Ipsogen) Breast Cancer Array (Randox)

DOI: 10.3310/hta20100 HEALTH TECHNOLOGY ASSESSMENT 2016 VOL. 20 NO. 10

OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer

Conclusions: OPTIMA prelim has achieved its aims of demonstrating that a large UK clinical trial of multiparameter assay-based selection of chemotherapy in hormone-sensitive early breast cancer is feasible. The economic analysis shows that a trial would be economically worthwhile for the NHS.

J Natl Cancer Inst. 2016 Apr 29;108(9). pii: djw050.

Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others.

Conclusions: Existing evidence on the comparative prognostic information provided by different tests suggests that current multiparameter tests provide broadly equivalent risk information for the population of women with estrogen receptor (ER)–positive breast cancers. However, for the individual patient, tests may provide differing risk categorization and subtype information.

Table 5. Number of tests agreeing with each test

No. of other tests agreed with test	Oncotype DX No. (%)	Prosigna No. (%)	MammaPrint No. (%)	IHC4 No. (%)	IHC4-AQUA No. (%)
4	119 (39.4)	119 (39.4)	119 (39.4)	119 (39.4)	119 (39.4)

TABLE 29 Intrinsic subtype predictions

Subtype group	BluePrint ($n = 298$)	Prosigna ($n = 299$)	MammaTyper Int.[a] ($n = 298$)	MammaTyper ($n = 298$)
Luminal A	181 (61%)	178 (60%)	186 (62%)	53 (18%)
Non-luminal A	117 (39%)	121 (40%)	112 (38%)	245 (82%)

a MammaTyper Int. combines luminal A and low-risk luminal B.

Value Health. 2017 Dec;20(10):1311-1318.

Value of Information Analysis of Multiparameter Tests for Chemotherapy in Early Breast Cancer: The OPTIMA Prelim Trial.

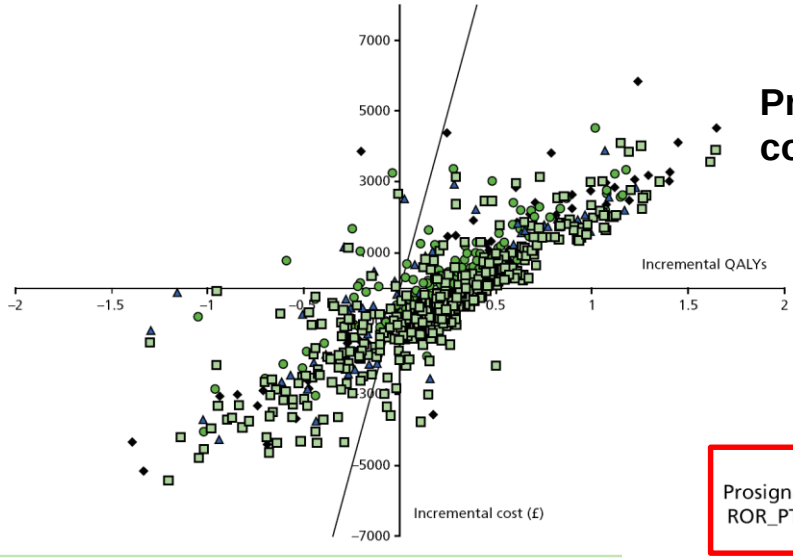


FIGURE 8 Scatterplot on the incremental cost-effectiveness plane, comparing each test included in the bas

Probability of test-directed chemotherapy to be more cost-effective than standard care: 86%

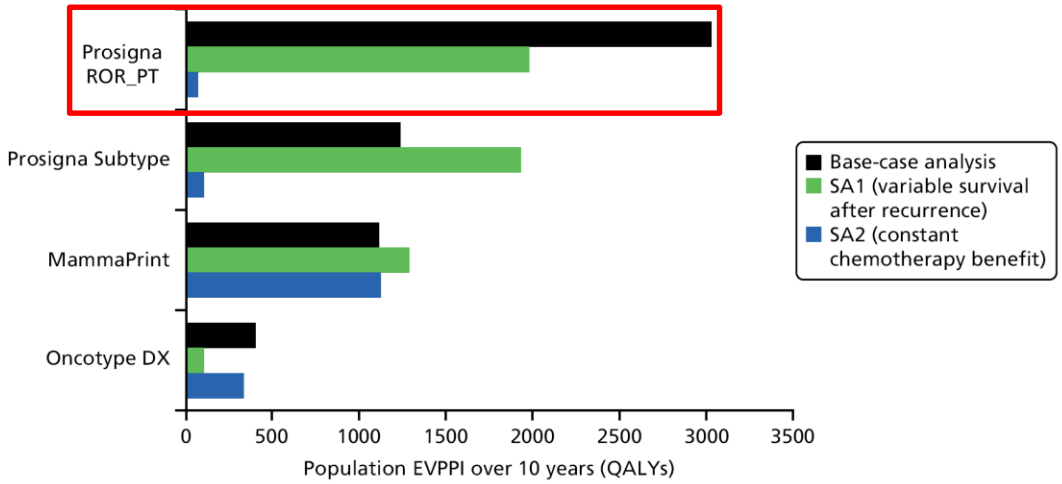
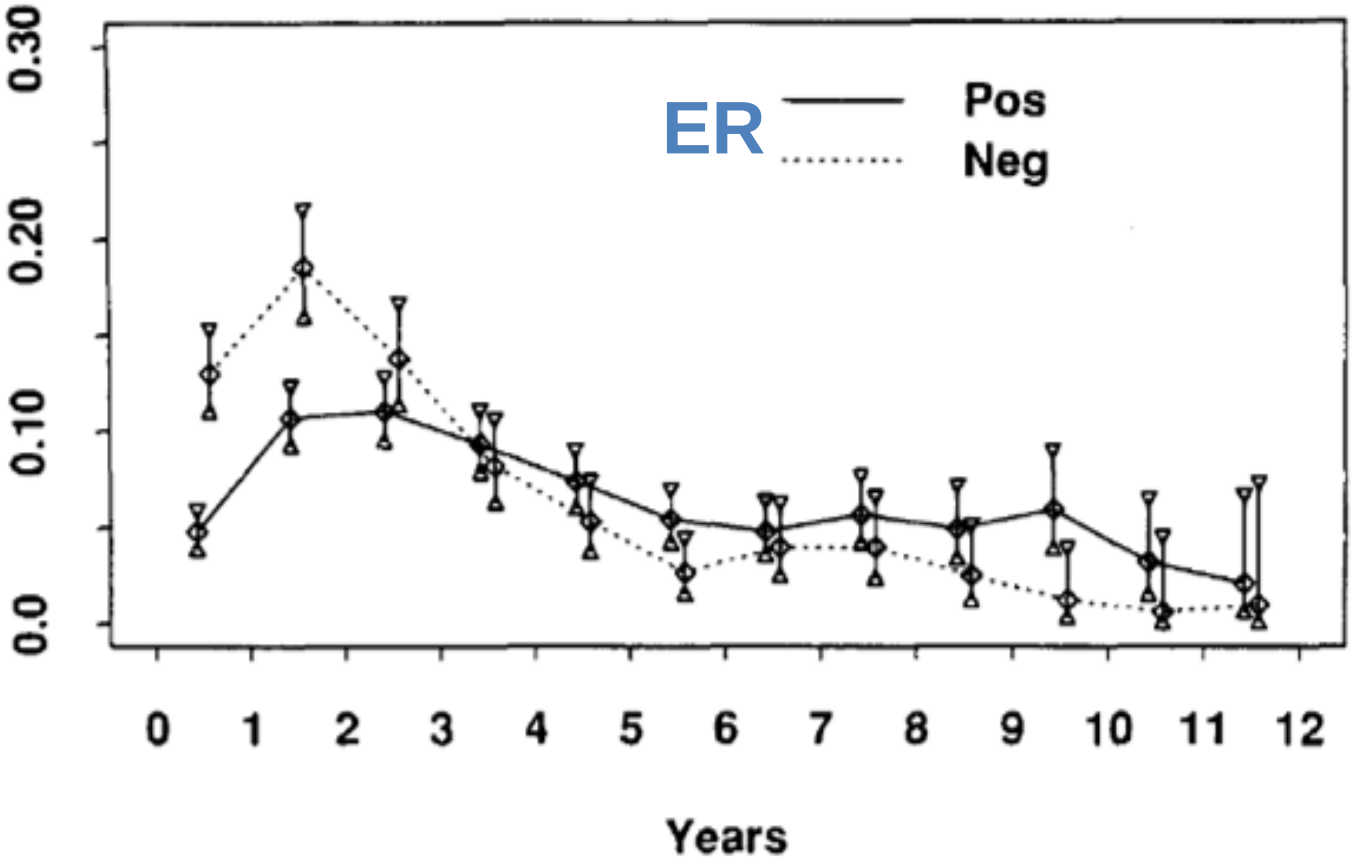


FIGURE 13 Value-of-information analysis for the base-case comparison and sensitivity analyses numbers 1 and 2. SA, sensitivity analysis.

Clinical Utility of Multigene Assay As a Predictive Biomarker(2)

For Prediction of Late Recurrence on Adjuvant Endocrine Therapy

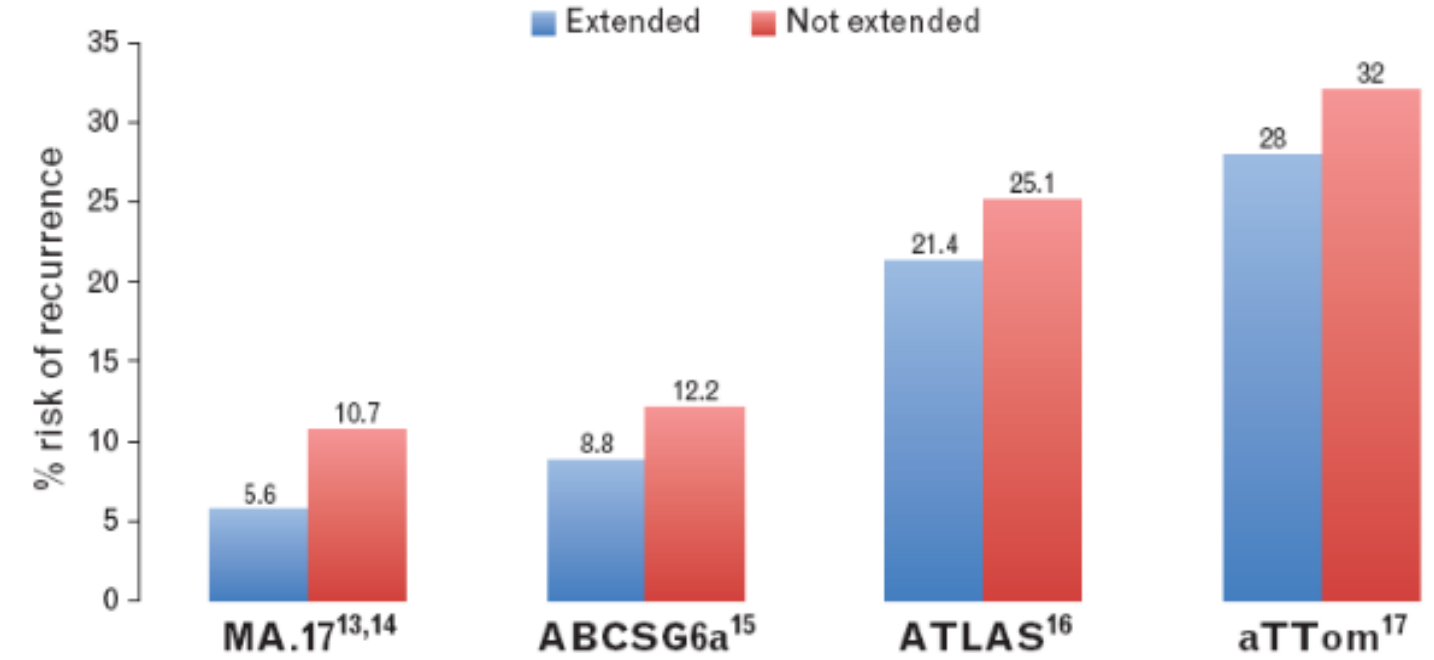
Late recurrence after surgery
with adjuvant therapy: analysis of ECOG trials



Annual Hazard Rates of Recurrence for Breast Cancer After Primary Therapy

J Clin Oncol 14:2738-2746. © 1996

Extended endocrine therapy & Late recurrence



Breast Care 2017;12:146–151

Comparison of MGAs for prediction of late distant recurrence

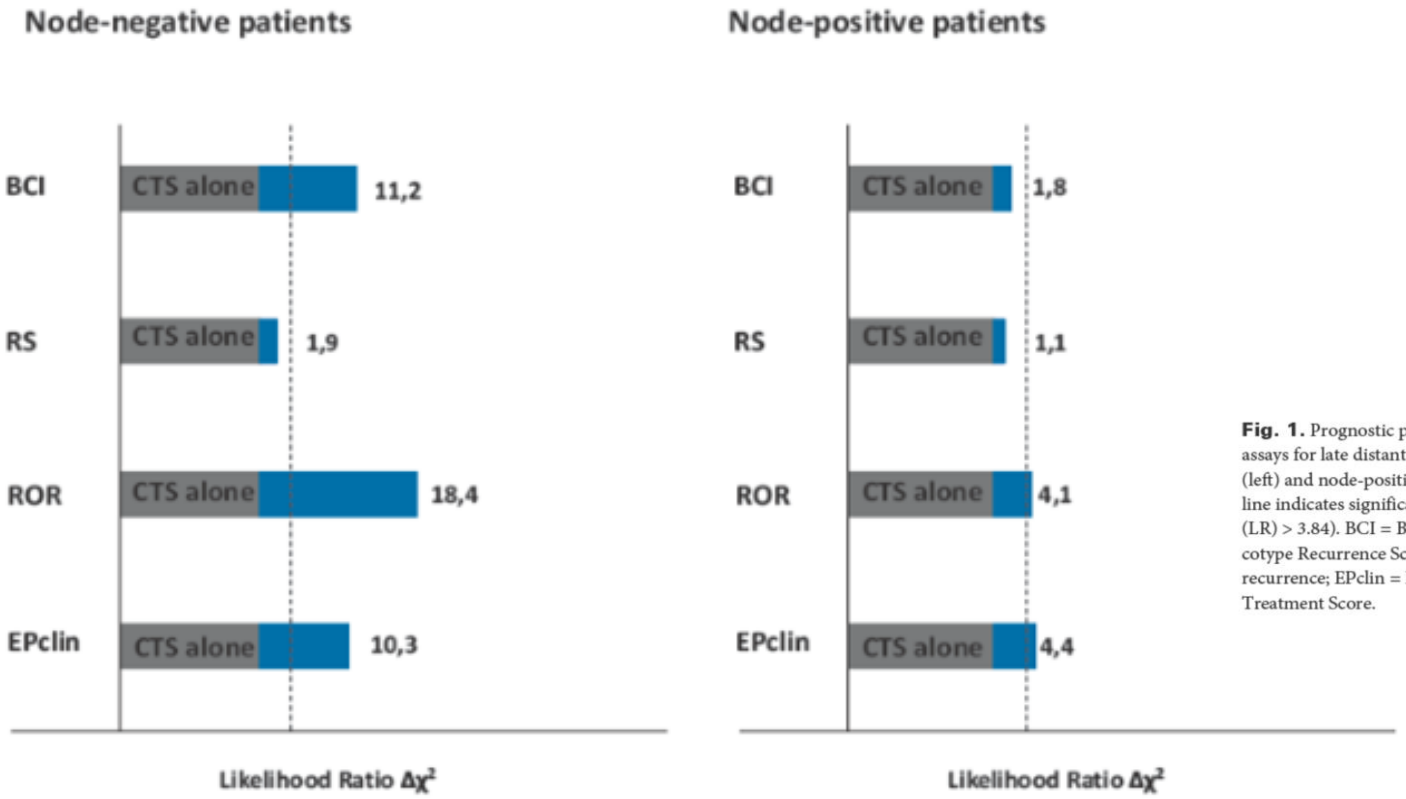


Fig. 1. Prognostic performance of multigene assays for late distant recurrence in node-negative (left) and node-positive (right) patients. Dotted line indicates significance level (Likelihood Ratio (LR) > 3.84). BCI = Breast Cancer Index; RS = Oncotype Recurrence Score; ROR = PAM50 risk of recurrence; EPclin = EndoPredict; CTS = Clinical Treatment Score.

Sestak I. Breast Care 2017 Jul;12(3):146-151.

Clinical Utility of Multigene Assay As a Predictive Biomarker(3)

For Safe Omission of Adjuvant Radiation Therapy

MGA for decision on adjuvant radiation therapy

Table 1 Ten-year local regional recurrence from breast conservation in biologically "low-risk" cases retrospectively analyzed from prospective trials

Trial samples	Median follow-up (years)	Selection criteria for "low risk"	10-year LRR (%)	
			Lumpectomy alone	Lumpectomy and RT
TBC trial [23]	10	Luminal A By IHC: ER, PR, HER2, CK5/6, EGFR, KI-67	7.3	3.3 ($P = 0.11$)
NSABP B-14/B-20 [25]	10–14	Oncotype RS ≤18	–	6.8
ECOG E2197 [26]	9.7	Oncotype RS ≤18	–	3.2
ABCSG 8 [27]	9.5	PAM50 ROR ≤57	–	1.9
ABCSG 8 [28]	6	EndoPredict low	11.1	0.2 ($P < 0.005$)
Netherlands Cancer Institute [29][a]	8.9	MammaPrint low risk	–	6.1

Curr Breast Cancer Rep (2017) 9:129–136

Ongoing trials to omit radiation therapy

Table 2 Clinical trials using biological selection criteria to enroll women with stage 1, ER/PR-positive, HER2-negative breast cancer to endocrine therapy alone *without radiotherapy* post lumpectomy

Trial	CA. gov identifier	Design	Biological selection	Eligible patient age (years)	Targeted accrual
LUMINA	NCT01791829	Phase II, single-arm observation	Luminal A by IHC		500
IDEA	NCT02400190	Phase II, single-arm observation	RS ≤18	50–69	250
PRECISION	NCT0265375	Phase II, single-arm observation	PAM50 ROR ≤40	55–65	1380
EXPERT	NCT02889874	Phase III randomized RT vs. observation	PAM50 Luminal A ROR ≤60	≥50	1167

EXamining PErsonalised Radiation Therapy for low-risk early breast cancer.
A randomised phase III trial of adjuvant radiation therapy versus observation following breast conserving surgery and endocrine therapy in patients with molecularly characterized luminal A early breast cancer.

Curr Breast Cancer Rep (2017) 9:129–136

SUMMARY & CONCLUSION

Multigene assay in breast cancer

- It has been used for more than a decade as an important biomarker for the prediction of patient's prognosis and of treatment response in adjuvant therapy of breast cancer.

- With this, the over- and under-treatments would be minimized in HR+, HER2-, node- early staged breast cancer.

- Ongoing prospective randomized trials of multigene assay would clarify and expand its roles in clinical practice for the treatment of breast cancer.

Thank you for your attention !