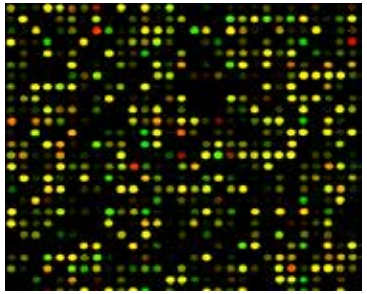
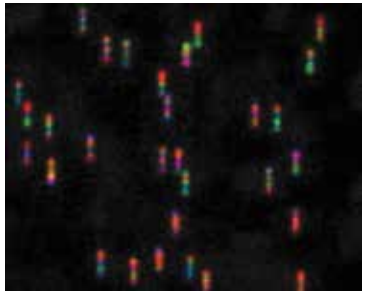
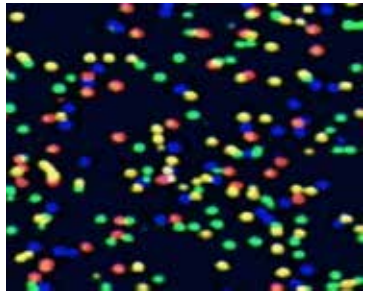




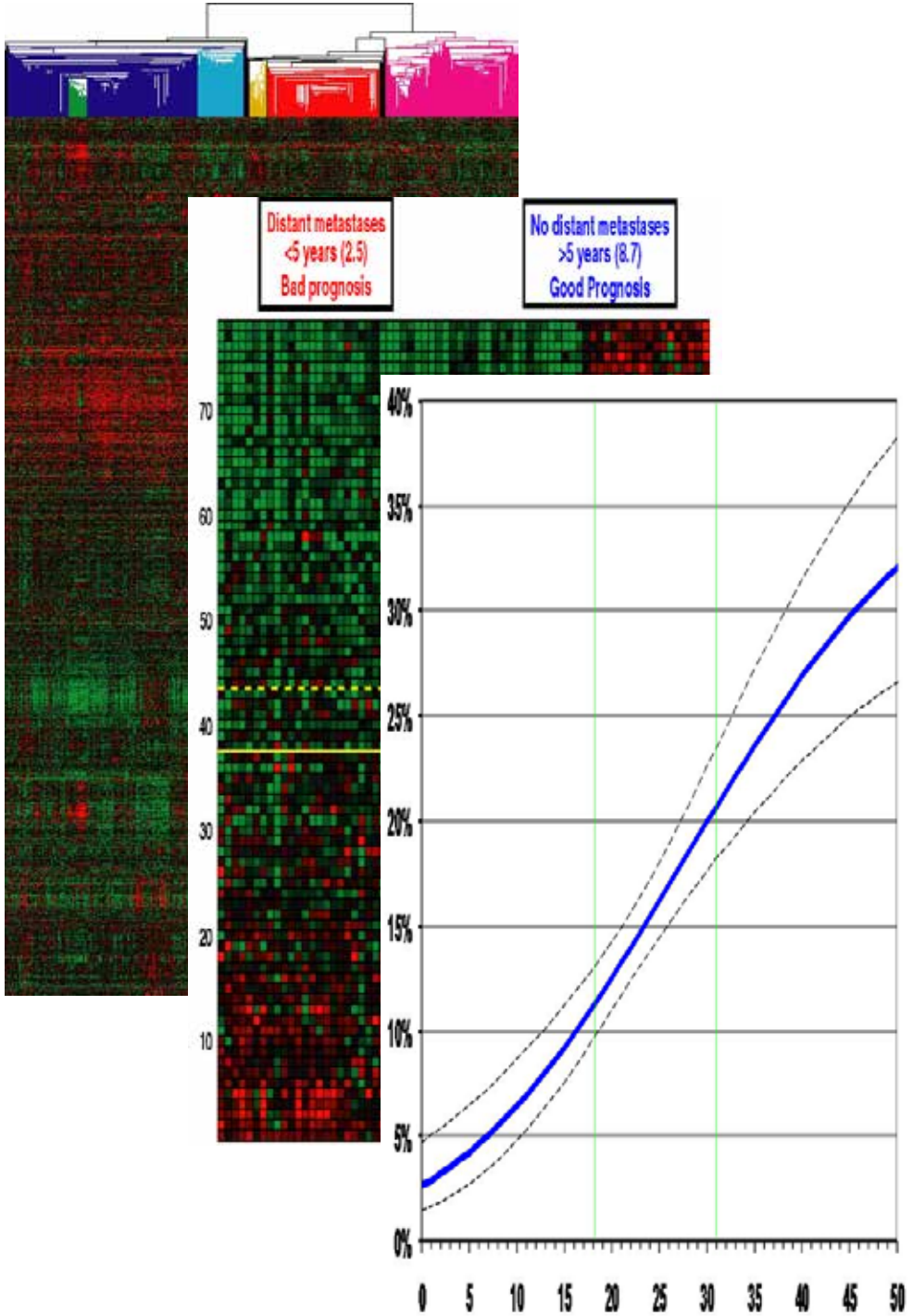
OVERVIEW OF GENE EXPRESSION-BASED TESTS IN EARLY BREAST CANCER

Aleix Prat, MD PhD

Medical Oncology Department
Hospital Clínic of Barcelona
University of Barcelona

Disclosures

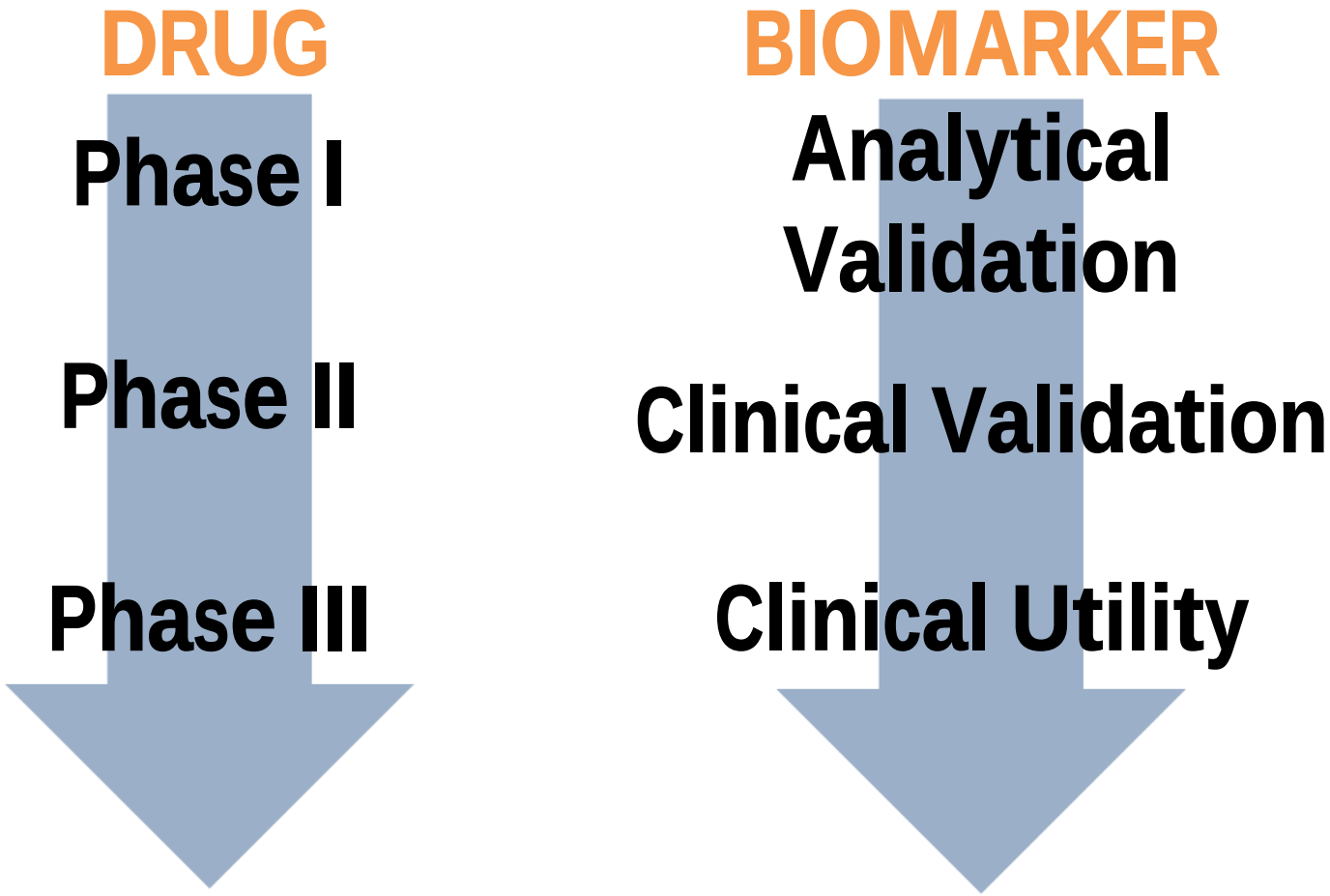
- Advisory role for Nanostring Technologies



Breast Cancer Gene Expression Profiling Tests Include:

1. **The PAM50 Intrinsic Subtypes: LumA, LumB, Basal-like, HER2-enriched (Wallden BMC 2015)**
2. **The PAM50 Risk of Recurrence (ROR) (Wallden BMC 2015)**
3. **OncotypeDX Recurrence Score (Paik et al., NEJM, 2004)**
4. **Mammaprint (van de Vijver et al., NEJM, 2002)**
5. **EndoPredict (Filipits et al., CCR 2011)**
6. **Breast Cancer Index: 2-gene ratio plus 5-gene proliferation (Ma et al., CCR 2008)**
7. **Genomic Grade Index (Sotiriou et al. JNCI 2006)**

Clinical Implementation of Drugs



READY FOR PRIME TIME

Clinical Implementation of Biomarkers

BIOMARKER

Analytical Validation

- Accuracy and Precision in measurement of analyte.
- Robustness.

Clinical Validation

- Correlation of score/classifier with clinical state or outcome.
  - e.g. biomarker identifies 2 prognostic groups.

Clinical Utility

- Actionable (could affect treatment).
- Use results for patient benefit.

Evaluation of Prognostic and Predictive Biomarkers. Levels of Evidence

Level	Characteristics	Use?
I	• Prospective Clinical Trial (PCT) designed to test marker • Consistent results from ≥ 2 PCTs not designed to test marker, but biomarker is tested in preplanned manner on both trials	Yes
II	• 1 PCT not designed for marker; biomarker analyses preplanned • ≥ 2 consistent results from Prospective Observational Cohorts (POC); preplanned analyses	Usually no
III	• 1 analysis POC; biomarker preplanned analyses	No
IV-V	• Unplanned biomarker analyses • Retrospectively ascertained cohorts	No

Richard M. Simon , Soonmyung Paik , Daniel F. Hayes, JNCI 2009

Are they analytically validated?

YES

Clinical Chemistry 53:6
1084–1091 (2007)

Cancer Diagnostics

Analytical Validation of the Oncotype DX Genomic Diagnostic Test for Recurrence Prognosis and Therapeutic Response Prediction in Node-Negative, Estrogen Receptor–Positive Breast Cancer

Maureen Cronin,* Chithra Sangli, Mei-Lan Liu, Mylan Pho, Debjani Dutta, Anhthu Nguyen, Jennie Jeong, Jenny Wu, Kim Clark Langone, and Drew Watson

Table 6. SD of the normalized expression measurement for the Oncotype DX assay, representing cumulative sources of process imprecision shown for each gene and the RS.

Official gene symbol	SD, reference normalized C_T
ACTB	0.01
BAG1	0.03
BCL2	0.09
CCNB1	0.09
CD68	0.10
SCUBE2	0.11
CTSL2	0.11
ESR1	0.05
GAPDH	0.25
GRB7	0.22
GSTM1	0.04
GUSB	0.03
ERBB2	0.07
MKI67	0.06
MYBL2	0.30
PGR	0.08
RPLP0	0.05
AURKA	0.10
MMP11	0.02
BIRC5	0.05
TFRC	0.04
RS	1.53

RS (0-100) SD < 2.0 units

BMC Genomics

BioMed Central

MammaPrint

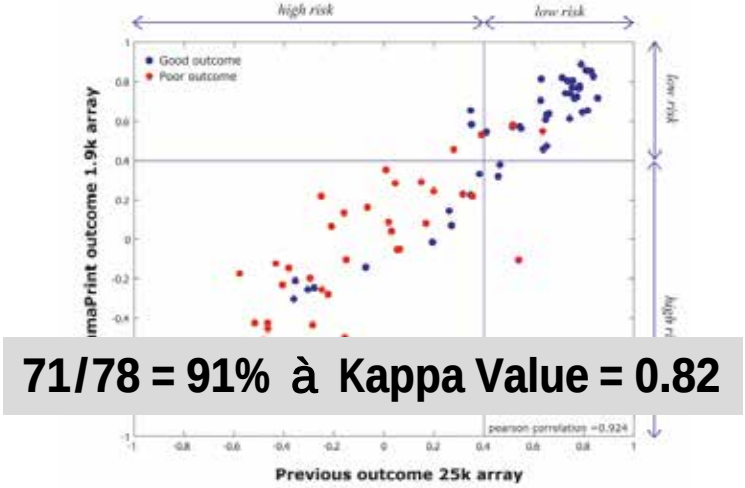
Methodology article

Open Access

Converting a breast cancer microarray signature into a high-throughput diagnostic test

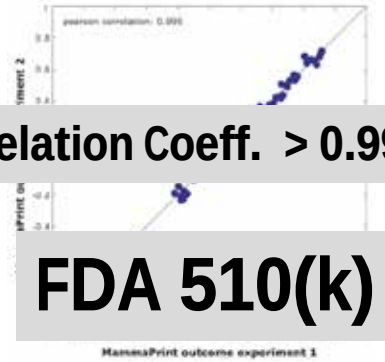
Annuska M Glas*[1], Arno Floore[1], Leonie JMJ Delahaye[1], Anke T Witteveen[1], Rob CF Pover[1], Niels Bakx[1], Jaana ST Lahti-Domenici[1], Tako J Bruinsma[1], Marc O Warmoes[1], René Bernards[1], Lodewyk FA Wessels[2] and Laura J Van 't Veer[1]

Customized mini-array reproducibility vs. original Agilent Arrays



71/78 = 91% à Kappa Value = 0.82

Customized mini-array reproducibility



Correlation Coeff. > 0.99

FDA 510(k)

MAMMAPRINT FFPE Assay

FDA 510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION

FF vs FFPE

Table 14 Second Validation Dataset – Agreement Analysis

	Second Validation Dataset (n=345)		
	Point Estimate	**N**	**95% CI**
PPA	86.6%	136/157	80.4% - 91.1%
NPA	91.5%	172/188	86.7% - 94.7%
Overall Concordance	89.3%	308/345	85.4% - 92.2%

PPA: positive percent agreement
NPA: negative percent agreement

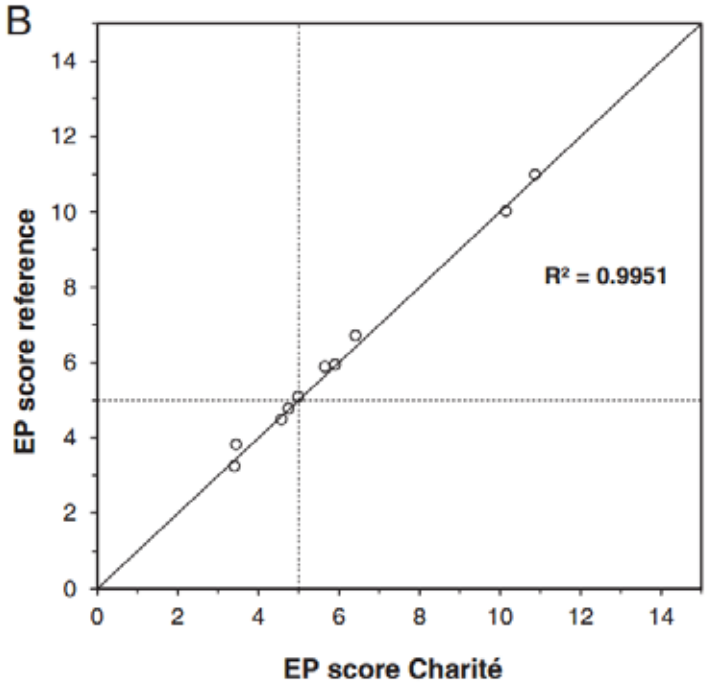
Analytical Validation of Decentralized Gene Expression-based tests (EndoPredict and PROSIGNA)

TECHNICAL ADVANCE Open Access

Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test

Ralf Kronenwett[1*], Kerstin Bohmann[1], Judith Prinzler[2], Bruno V Sinn[2], Franziska Haufe[1], Claudia Roth[1], Manuela Averdick[1], Tanja Ropers[1], Claudia Windbergs[1], Jan C Brase[1], Karsten E Weber[1], Karin Fisch[1], Berit M Müller[2], Marcus Schmidt[3], Martin Filipits[4], Peter Dubsky[5], Christoph Petry[1], Manfred Dietel[2] and Carsten Denkert[2]

- EP (0-15) SD (from RNA) = 0.14



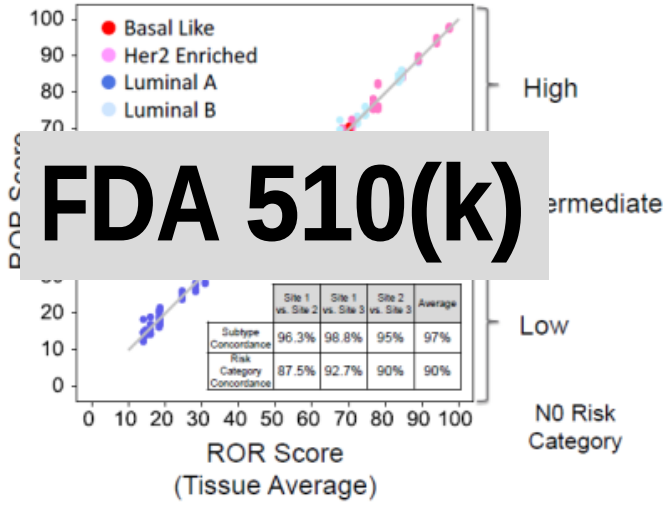
Kronenwett et al. BMC Cancer 2012

TECHNICAL ADVANCE Open Access

Analytical validation of the PAM50-based Prosigna Breast Cancer Prognostic Gene Signature Assay and nCounter Analysis System using formalin-fixed paraffin-embedded breast tumor specimens

Torsten Nielsen[1,4*], Brett Wallden[2], Carl Schaper[3], Sean Ferree[2], Shuzhen Liu[1], Dongxia Gao[1], Garrett Barry[1], Naeem Dowidar[2], Malini Maysuria[2] and James Storhoff[2]

- Subtype concordance= 97-100%
- ROR (0-100) SD (from RNA) = 0.82
- ROR (0-100) SD (from tissue) = 2.90



FDA 510(k)

Torsten et al. BMC Genomics 2014

Can these tests help us identify patients who do not need adjuvant chemotherapy because of their low risk of relapsing?

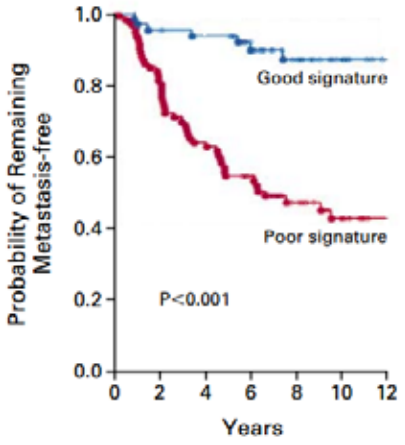
YES

Predicting Baseline Prognosis

Identification of patients with HR+/HER2-negative disease (T1-2/0-3 N+):

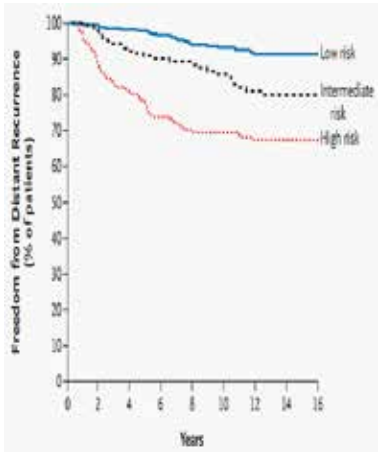
- *Who can be spared adjuvant multi-agent chemotherapy due to their low risk (<10%) of distant recurrence at 10-years with endocrine therapy-only.*

MammaPrint



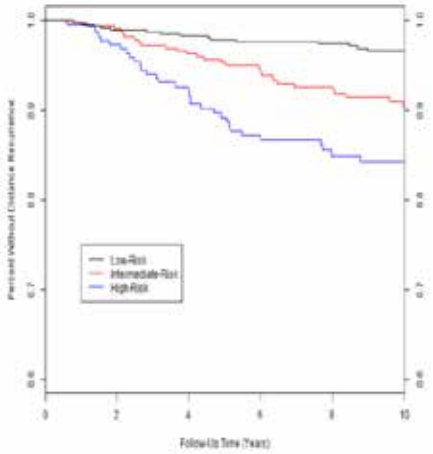
Vijver NEJM 2002

OncotypeDX



Paik NEJM 2006

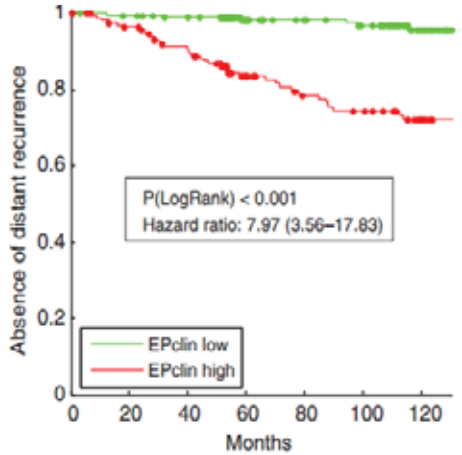
PAM50 ROR



Dowsett JCO 2013

(includes tumor size)

EndoPredict

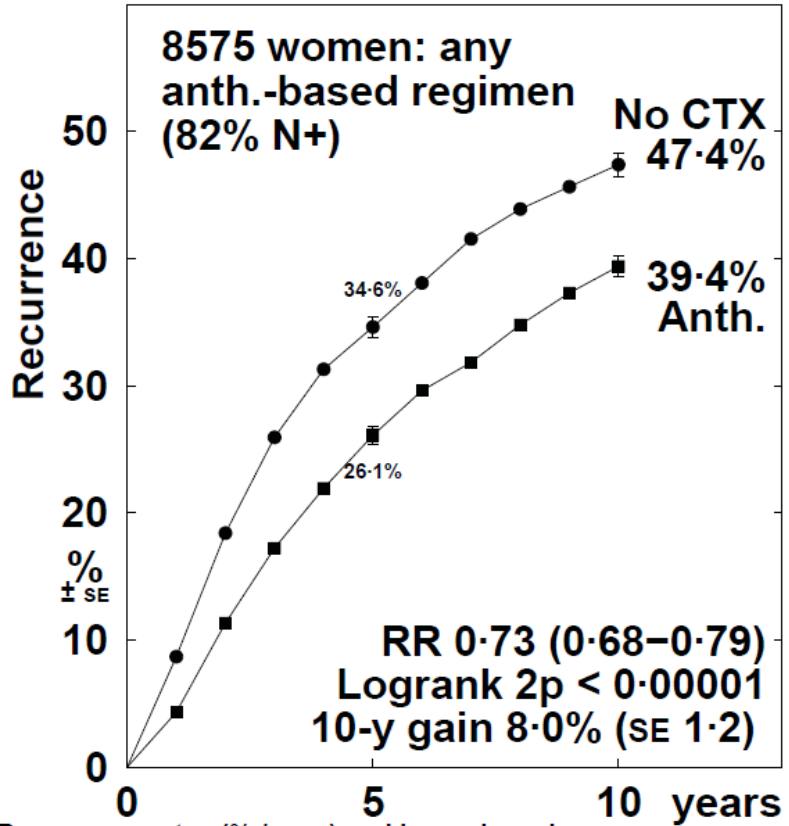


Filipits CCR 2011

(includes tumor size and nodal status)

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	6·14 (1179 / 19190)	4·06 (487 / 11981)	2·91 (161 / 5530)
No CTX	9·06 (1259 / 13899)	4·56 (365 / 8011)	3·87 (159 / 4104)
Rate ratio	0·69 SE 0·04	0·89 SE 0·07	0·72 SE 0·11
(O−E) / V	−185·2 / 489·8	−20·0 / 174·7	−21·2 / 65·5

- 1/3 breast cancer mortality reduction
- Depend on absolute risks without chemotherapy.
- Proportional risk reductions were little affected by age, nodal status, tumor size, estrogen receptor status, or tamoxifen use.
- However, gene expression-based tests were not evaluated.

10-year Absolute Risk without chemo	10-year Absolute Benefit from chemo	10-year Risk with chemo
10%	3%	7%
20%	6%	14%
30%	9%	21%

Lancet 2012

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

HR+/HER2-neg and NODE-negative

	INDICATION	Evidence Quality	Recommendation Strenght
OncotypeDX	YES	HIGH	STRONG
PAM50 ROR	YES	HIGH	STRONG
EndoPredict	YES	INTERMEDIATE	MODERATE
MammaPrint	NO	INTERMEDIATE	MODERATE

New data!

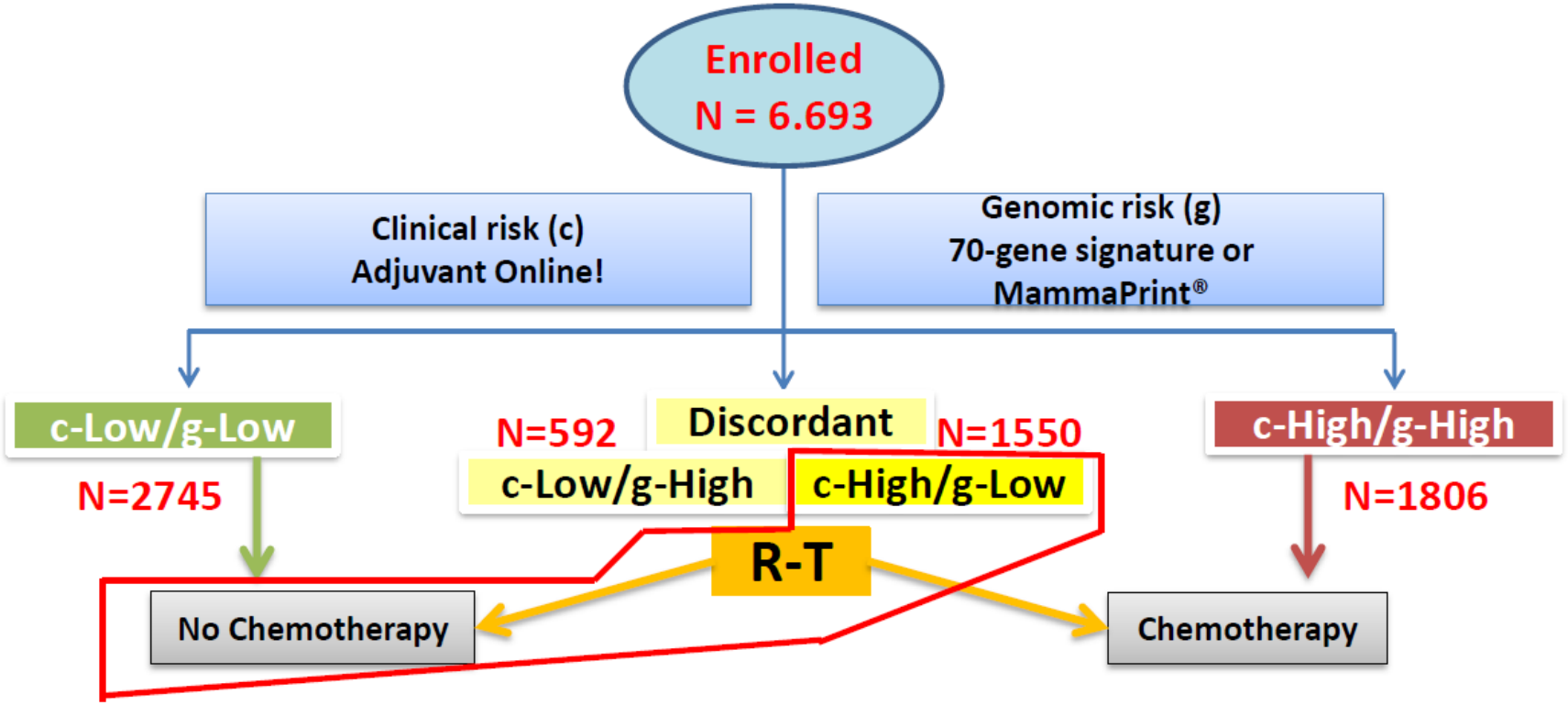
TransATAC

MINDACT

J Clin Oncol 2016

MINDACT

The primary analysis population



Primary endpoint: Distant metastasis free survival (DMFS) at 5 years

Null hypothesis: 5-year DMFS rate in PT population = 92%

ha: 2.5% (1-sided)

Power: 80% when true 5-year DMFS rate=95%

Cardoso et al. NEJM 2016

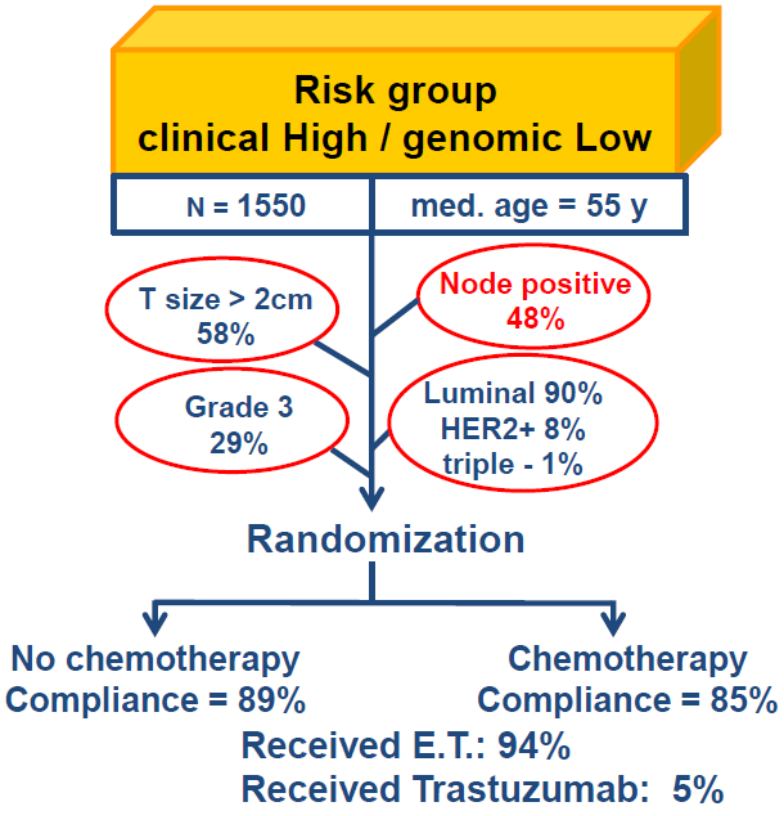
MINDACT – Clinical Risk Definition

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high

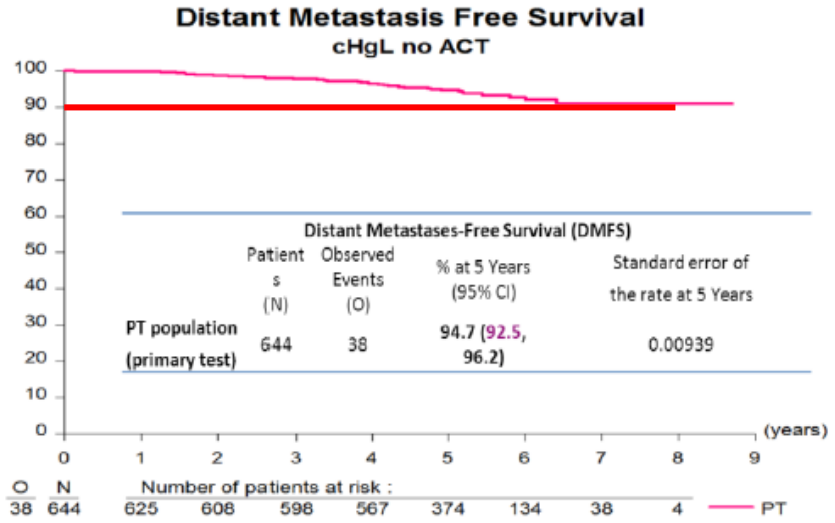
Cardoso et al. NEJM 2016

Clinical outcome of the MINDACT population at 5y median follow-up

B) DISCORDANT RISK GROUPS: PRIMARY TEST



The primary statistical test (DMFS at 5Y)



Null Hypothesis: set at 92%

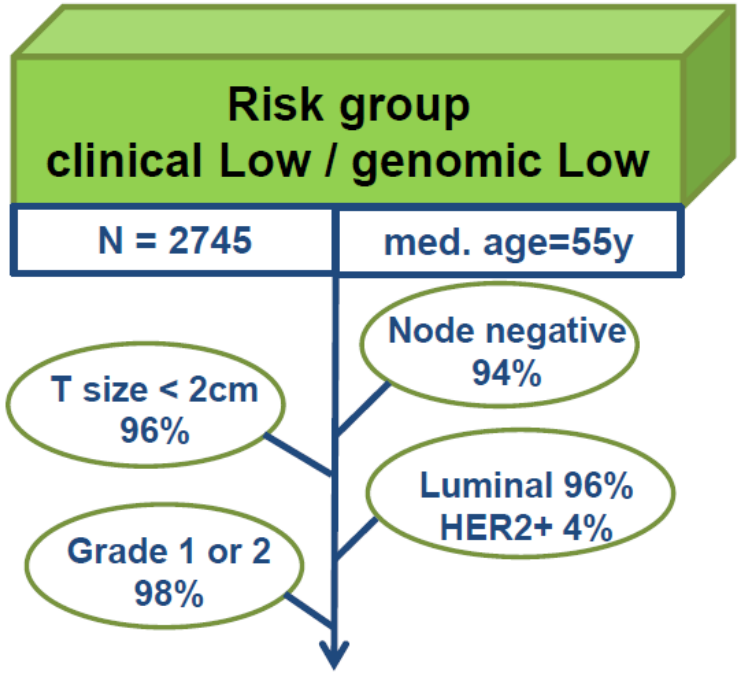
Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2%

from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

Cardoso et al. NEJM 2016

MINDACT
clinical low risk / genomic low risk

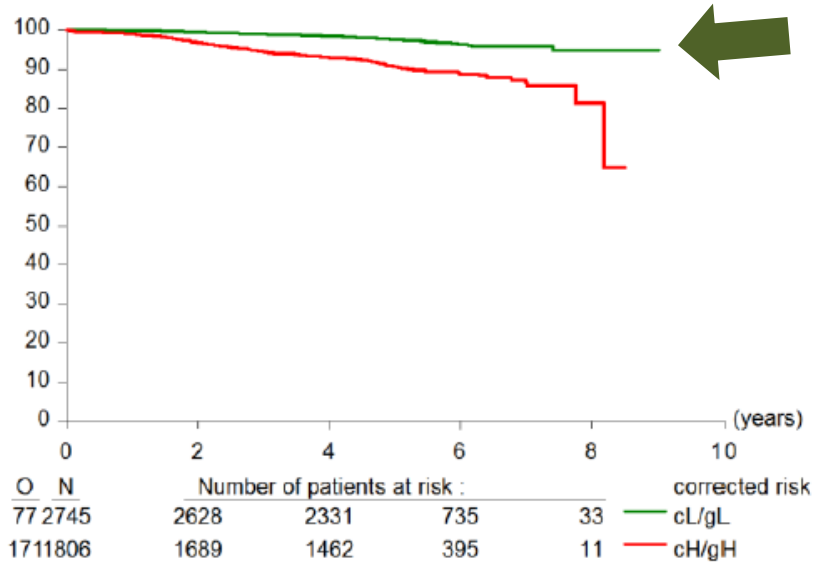


Assigned:
NO CHEMOTHERAPY

Compliance = 99%

(Received Endocrine therapy: 79%)

DMFS



% at 5y (95% CI)

cL/gL **97.6** (96.9 – 98.1)

Cardoso et al. NEJM 2016

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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HR+/HER2-neg and NODE-negative

	INDICATION	Evidence Quality	Recommendation Strenght
OncotypeDX	YES	HIGH	STRONG
PAM50 ROR	YES	HIGH	STRONG
EndoPredict	YES	INTERMEDIATE	MODERATE
MammaPrint	NO	INTERMEDIATE	MODERATE

New data!

TransATAC

MINDACT

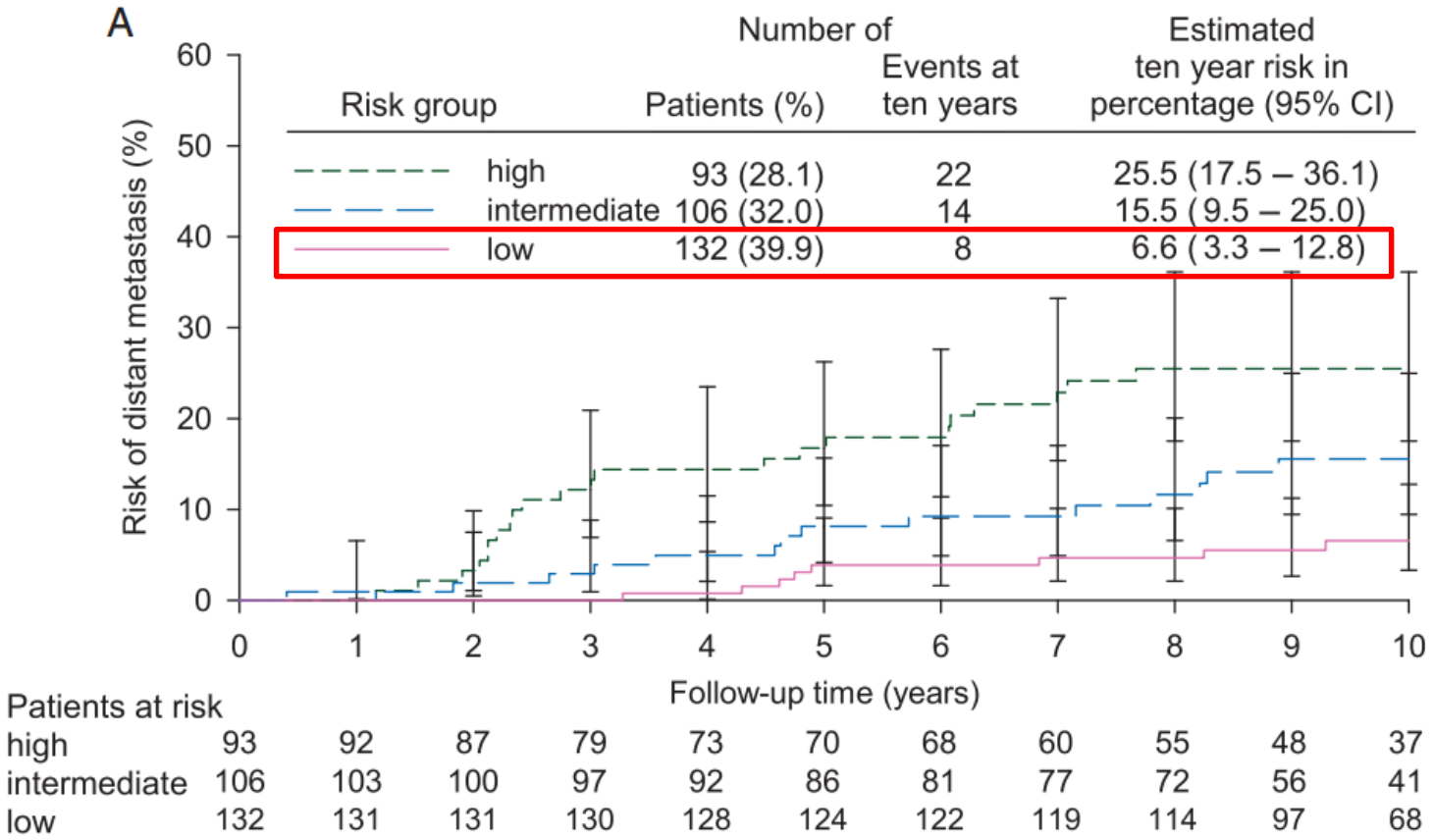
HR+/HER2-neg and NODE-positive

	INDICATION	Evidence Quality	Recommendation Strenght
OncotypeDX	NO	INTERMEDIATE	MODERATE
PAM50 ROR	NO	INTERMEDIATE	MODERATE
EndoPredict	NO	INSUFFICIENT	MODERATE
MammaPrint	NO	INTERMEDIATE	MODERATE

J Clin Oncol 2016

PROSIGNA within HR+/HER2-neg and 1 positive node

- **TransATAC + ABCSG08 combined analysis**
- **N=331 1N+ and 212 2-3N+**
- **5-years of endocrine therapy and no chemotherapy**



Gnant et al. Annals Oncol 2015

Should we use Ki67 IHC to identify low risk outcome patients who do not need adjuvant chemotherapy?

NO

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

Guide choice on adjuvant chemotherapy

	INDICATION	Evidence Quality	Recommendation Strenght
Ki67 IHC	NO	INTERMEDIATE	MODERATE
IHC4	NO	INTERMEDIATE	MODERATE

IHC for Ki-67 analysis lacks reproducibility across laboratories and, therefore, cannot be consistently interpreted when performed in a broad range of laboratories.

J Clin Oncol 2016

Can these tests help us determine the benefit of adjuvant chemotherapy?

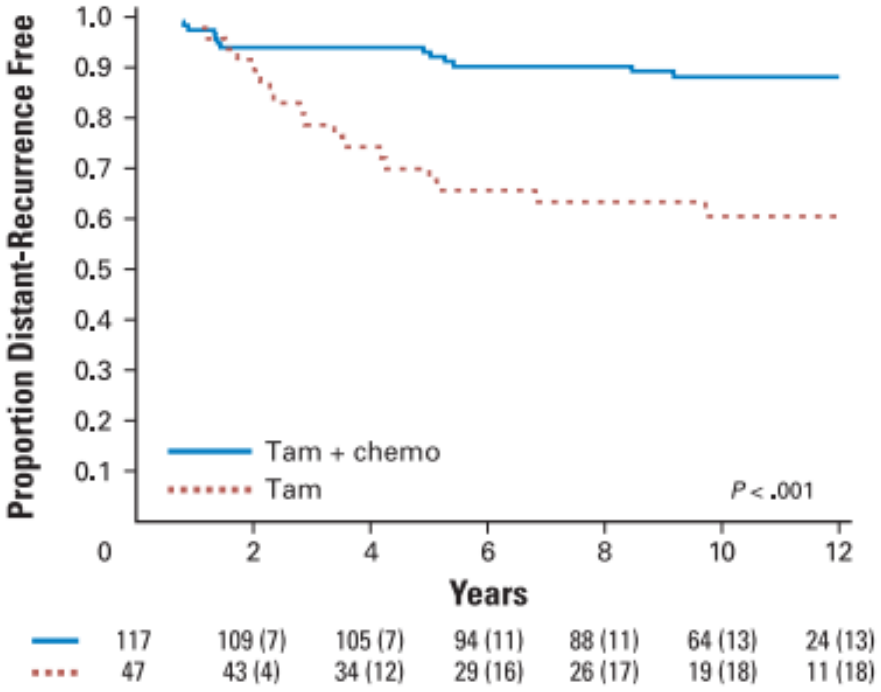
Maybe

NSABP-B20 subanalysis

Paik et al. JCO 2006

OncotypeDX RS HIGH RISK

N=651 ; ER+/NODE-negative



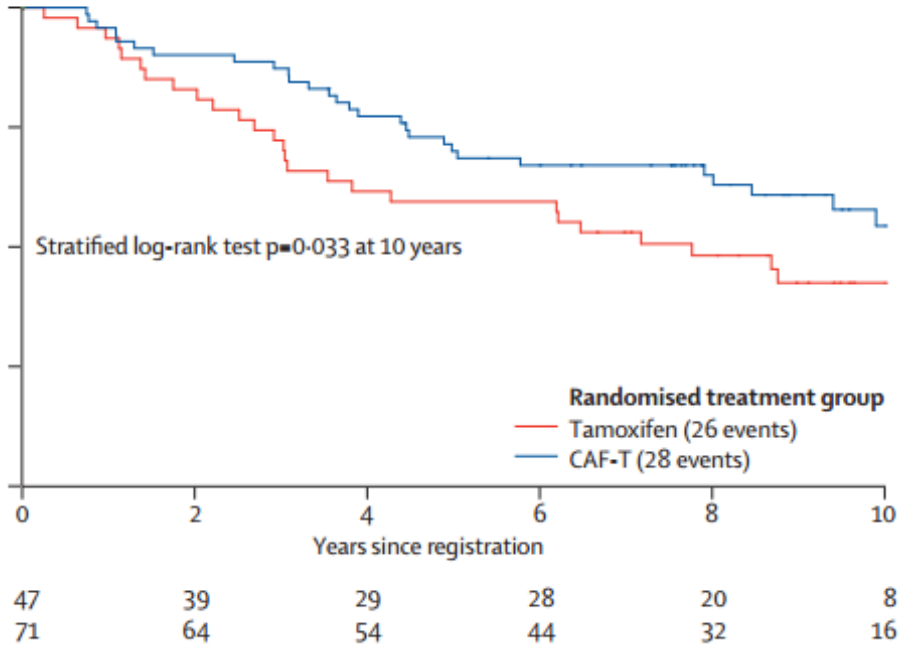
NSABP-B20 data are confounded by the dataset originally used to generate the assay.

SWOG8814 subanalysis

Albain et al. Lancet Oncol 2010

OncotypeDX RS HIGH RISK

N=367 ; ER+/NODE+

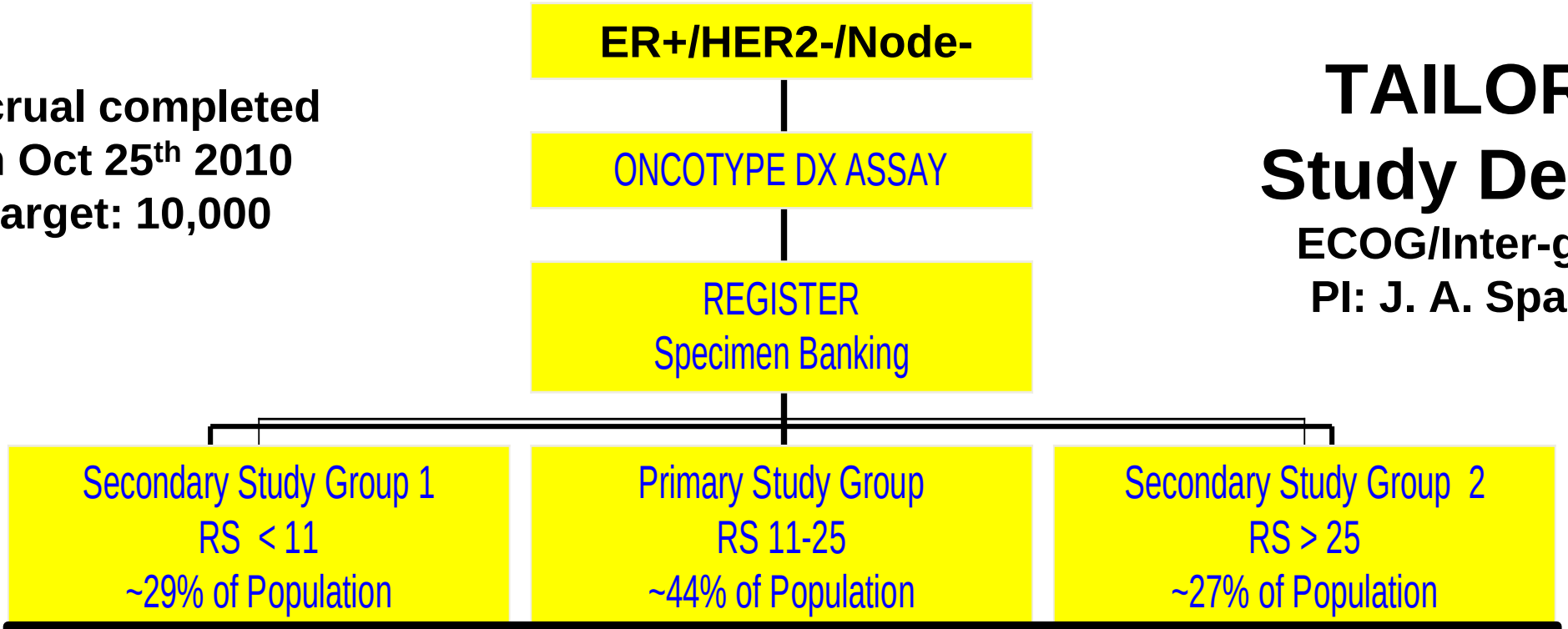


SWOG8814 data is hypothesis generating: small sample set and no additional prediction beyond 5 years.

TAILORx Study Design

ECOG/Inter-group
PI: J. A. Sparano

Accrual completed on Oct 25th 2010
Target: 10,000



Primary Objective:

- Non-inferiority study within the intermediate group
- Null hypothesis: no treatment diferences
- No chemotherapy arm (>87% 5-year DFS)
- Chemotherapy arm (90% 5-year DFS).
- Type 1 error: 10%; Type 2 error: 5%
- 95% power

5-year 99.
69% <1.9
Sparano

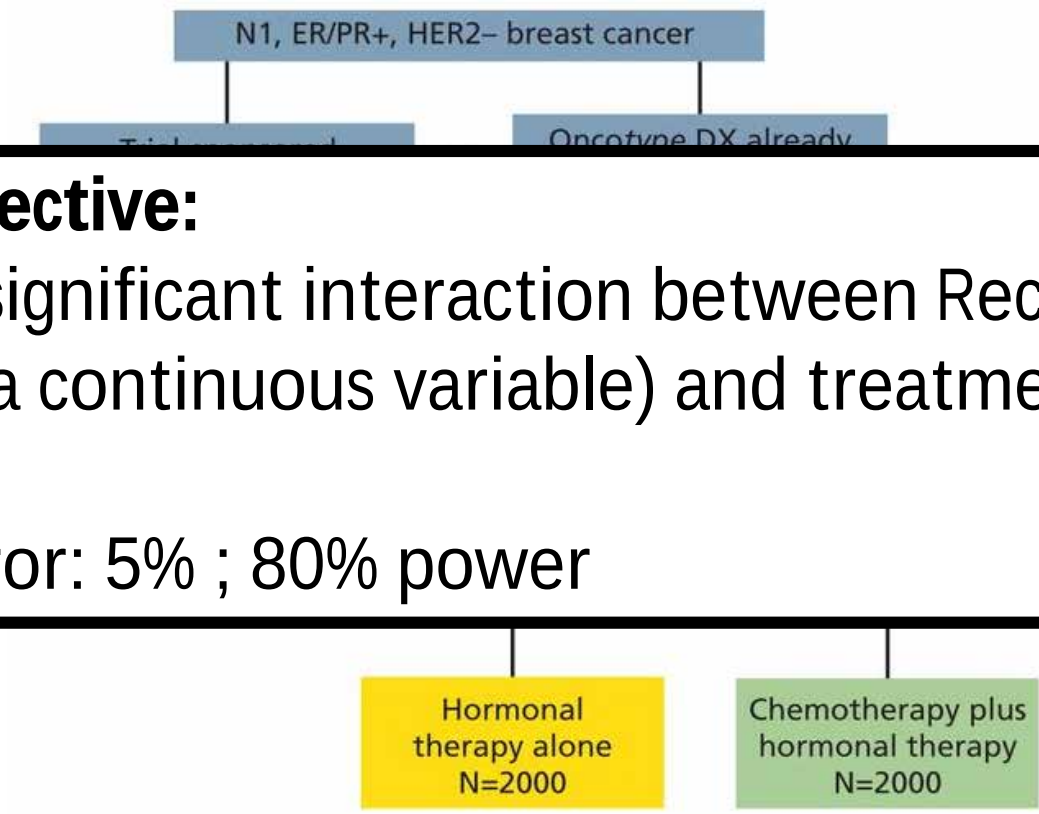
SWOG RxPONDER Trial (S1007): Patient Information

Taking part in RxPONDER

Thank you for your interest in the RxPONDER (*riz-POND-er*) clinical trial.

RxPONDER *a clinical trial*
Rx for Positive Node, Endocrine Responsive Breast Cancer

A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, HR+/HER2-negative and HER2-Negative Breast Cancer With Recurrence Score (RS) of 25 or Less.
ClinicalTrials.gov Identifier: NCT01272037
Opened 2011, Estimated Accrual = 4000



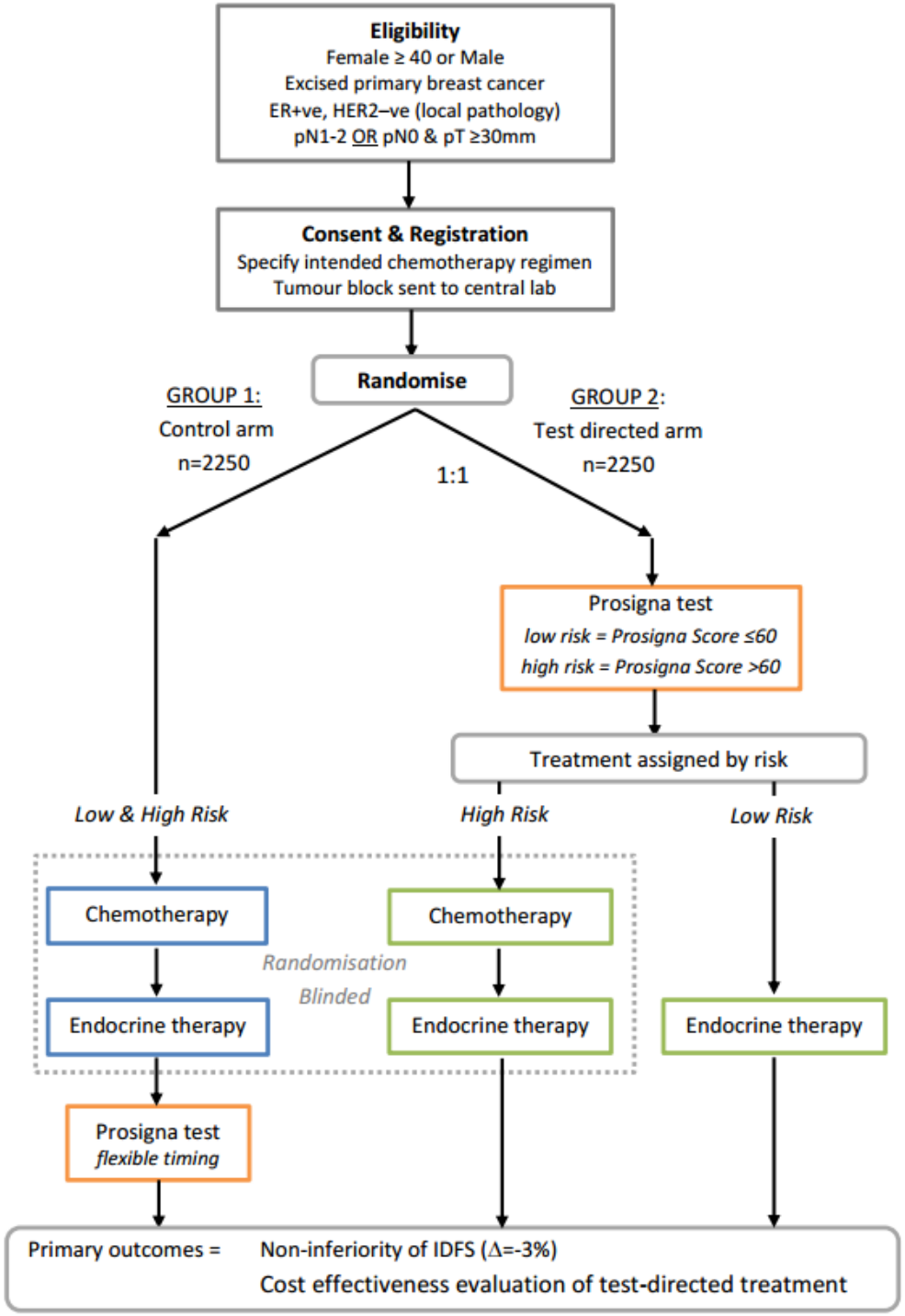
Primary Objective:

- To find a significant interaction between Recurrence Score (as a continuous variable) and treatment
- DFS
- Type 1 error: 5% ; 80% power

optima

personalised treatment of breast cancer

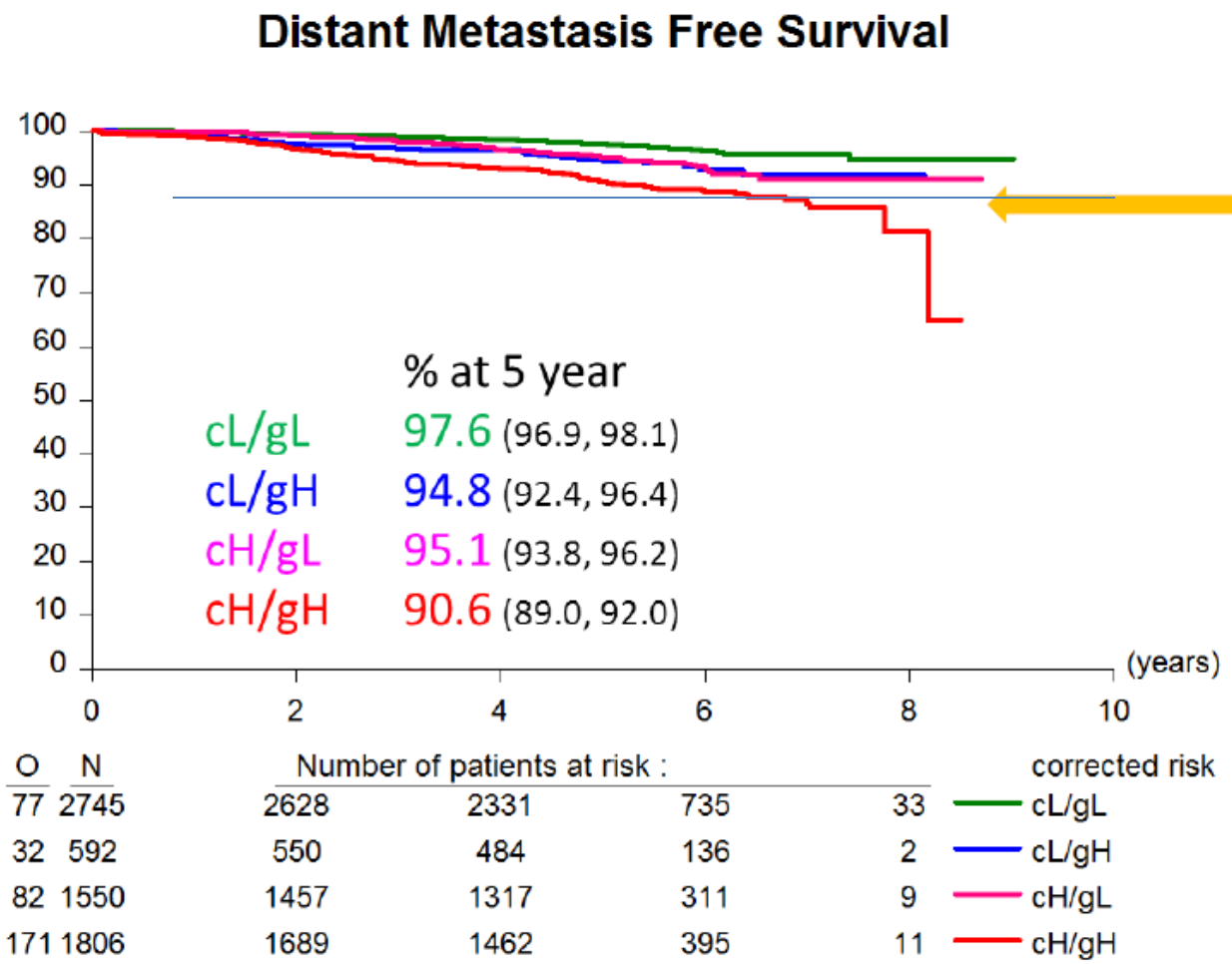
- N=4,500
- HR+/HER2-negative
- pN1-2 or pT ≥3 cm
- Non-inferiority (delta 3%, 85% power)
  - 5-year DFS 82% without chemotherapy
- PROSIGNA will be used (cutpoint 60)
  - High risk
  - Low/Intermediate risk



http://www.nets.nihr.ac.uk/projects/hta/1034501

Clinical outcome of the MINDACT population at 5y median follow-up

DMFS IN ALL 4 RISK GROUPS



from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

Cardoso et al. NEJM 2016

MINDACT – secondary endpoints

Efficacy: CT vs no CT in discordant risk group c-Low/g-High per protocol analysis

c-Low/g-High CT vs no CT per protocol population

	Treatment received	Patients	Observed Events	% at 5 Year(s) (95% CI)	Hazard Ratio (adjusted Cox model) (95% CI)	p-value (adjusted logrank)
DMFS	CT	224	11	**96.1** (92.4, 98.1)	**0.90** (0.40,2.01)	0.798
	no CT	254	14	**93.9** (89.6, 96.5)	1.00	
DFS	CT	224	17	**92.7** (87.9, 95.7)	**0.74** (0.40,1.39)	0.355
	no CT	254	25	**90.5** (85.7, 93.8)	1.00	
OS	CT	224	5	**98.1** (94.9, 99.3)	**0.72** (0.23,2.24)	0.572
	no CT	254	8	**97.0** (93.8, 98.6)	1.00	

EORTC The future of cancer therapy

BIG Breast International Group

TRANSBIG

from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

Trial not powered for the comparisons of yes or no chemotherapy

Cardoso et al. NEJM 2016

MINDACT – secondary endpoints

Efficacy: CT vs no CT in discordant risk group c-High/g-Low per protocol analysis

c-High/g-Low CT vs no CT per protocol population

	Treatment received	Patients	Observed Events	% at 5 Year(s) (95% CI)	Hazard Ratio (adjusted Cox model) (95% CI)	p-value (adjusted logrank)
DMFS	CT	592	22	**96.7** (94.7, 98.0)	**0.65** (0.38,1.10)	0.106
	no CT	636	37	**94.8** (92.6, 96.3)	1.00	
DFS	CT	592	39	**93.3** (90.7, 95.2)	**0.64** (0.43,0.95)	0.026
	no CT	636	66	**90.3** (87.6, 92.4)	1.00	
OS	CT	592	10	**98.8** (97.4, 99.5)	**0.63** (0.29,1.37)	0.245
	no CT	636	18	**97.3** (95.6, 98.4)	1.00	

EORTC The future of cancer therapy

BIG Breast International Group

TRANSBIG

from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

Trial not powered for the comparisons of yes or no chemotherapy

Cardoso et al. NEJM 2016

Can these tests identify patients that may be spared extended endocrine therapy?

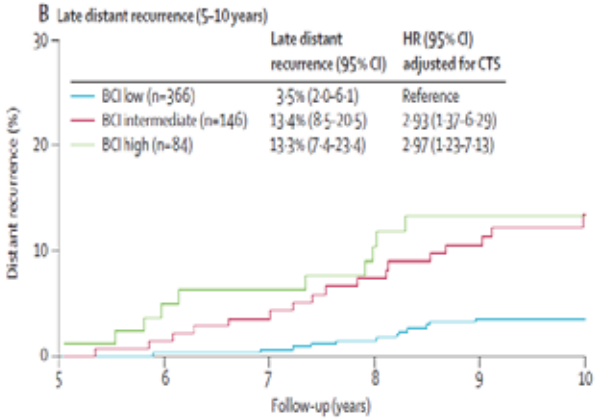
Maybe

Predicting Late Recurrence

To identify a group of patients with HR+/HER2-negative disease (T1-2/0-3 N+):

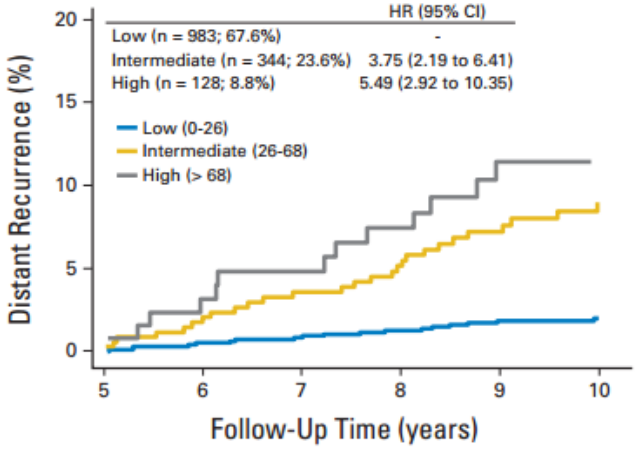
- ***That may be spared extended endocrine therapy (5-10 years) due to their low risk of recurrence***

BC Index



Sgroi Lancet Oncol 2013

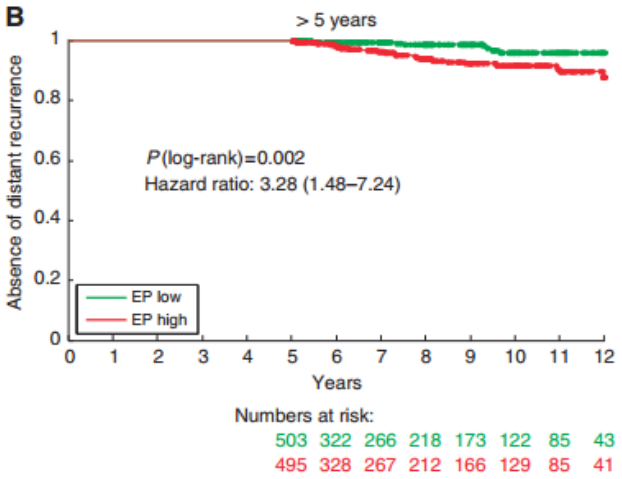
PAM50 ROR



Sestak JCO 2015

(includes tumor size)

EndoPredict



Dubsky BJC 2013

(includes tumor size and nodal status)

Factors Predicting Late Recurrence for Estrogen Receptor–Positive Breast Cancer

Ivana Sestak, Mitch Dowsett, Lila Zabaglo, Elena Lopez-Knowles, Sean Ferree, J. Wayne Cowens, Jack Cuzick

Table 3. Likelihood (χ^2) for distant recurrence for all scores according to subgroup*

	0 to 5 years		5 to 10 years	
	Univariate	Multivariable	Univariate	Multivariable
Scores	χ^2 (*P*)	χ^2 (*P*)	χ^2 (*P*)	χ^2 (*P*)
	HER2-negative/node-negative (n = 615)			
CTS	14.06 (<.001)	—	20.12 (<.001)	—
IHC4	19.23 (<.001)	12.06 (<.001)	9.97 (.002)	3.89 (.05)
RS	13.52 (<.001)	6.84 (.008)	7.99 (.005)	2.23 (.1)
ROR	19.65 (<.001)	8.61 (.008)	28.73 (<.001)	13.85 (<.001)

- **The ROR score was the strongest molecular prognostic** factor in the late follow-up period, whereas IHC4 and OncotypeDX RS were only weakly prognostic in this period.

JNCI 2013

The EndoPredict score provides prognostic information on late distant metastases in ER + /HER2 − breast cancer patients

P Dubsky*[,1], J C Brase[2], R Jakesz[1], M Rudas[3], C F Singer[4], R Greil[5], O Dietze[6], I Luisser[7], E Klug[8], R Sedivy[9], M Bachner[10], D Mayr[11], M Schmidt[12], M C Gehrmann[13], C Petry[2], K E Weber[2], K Fisch[2], R Kronenwett[2], M Gnant[1] and M Filipits[14] on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)

N=1,702 (ABCSG6/8)

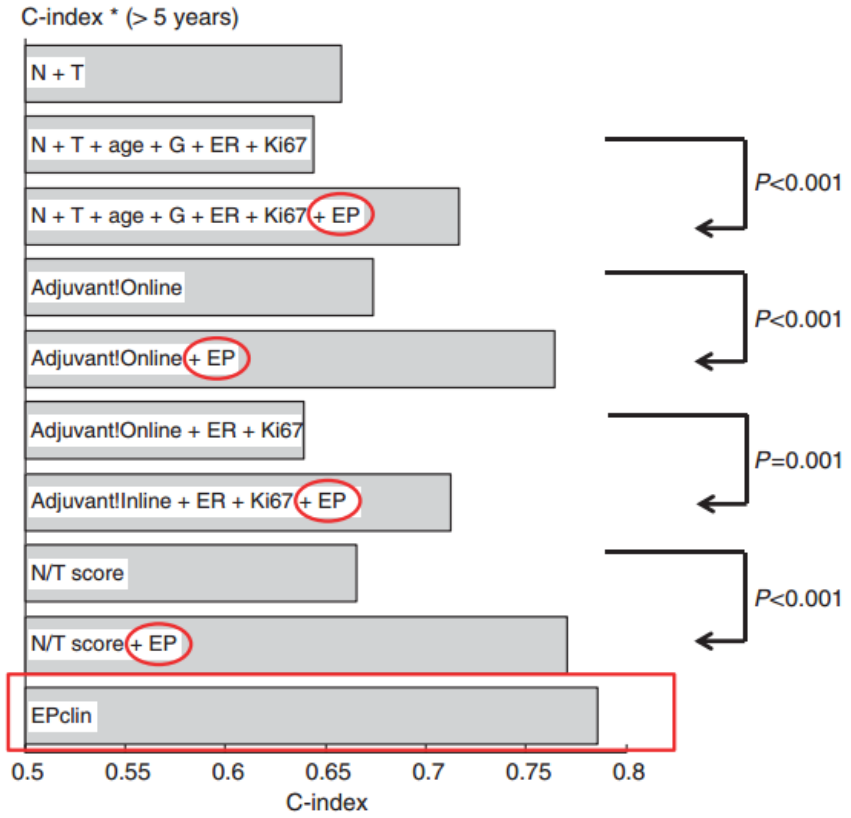


Table 1. Multivariate Cox proportional hazard models for estimating the contribution of variables to predict distant recurrence in the time interval 0–5 years and after 5 years (1702 ER + /HER2 − tumours, ABCSG6/8)

Variable	0–5 years unit HR (95% CI)	*P*-value	> 5 years unit HR (95% CI)	*P*-value
EP	1.20 (1.10–1.31)	<0.001	1.28 (1.10–1.48)	0.001
Age	1.03 (1.00–1.06)	0.032	0.97 (0.93–1.02)	0.264
Nodal status	2.15 (1.67–2.77)	<0.001	2.45 (1.58–3.81)	<0.001
Tumour size	1.26 (0.94–1.70)	0.121	1.11 (0.67–1.86)	0.679
Ki67	1.01 (0.99–1.03)	0.171	1.01 (0.97–1.05)	0.761
Grade	1.21 (0.77–1.90)	0.414	0.64 (0.32–1.28)	0.210
Treatment arm	0.95 (0.61–1.48)	0.807	0.91 (0.40–2.09)	0.827

Abbreviations: CI = confidence interval; ER = oestrogen receptor; HR = hazard ratio.

Dubsky et al. BJC 2013

Distant Late Recurrence Rates of Low Risk Groups

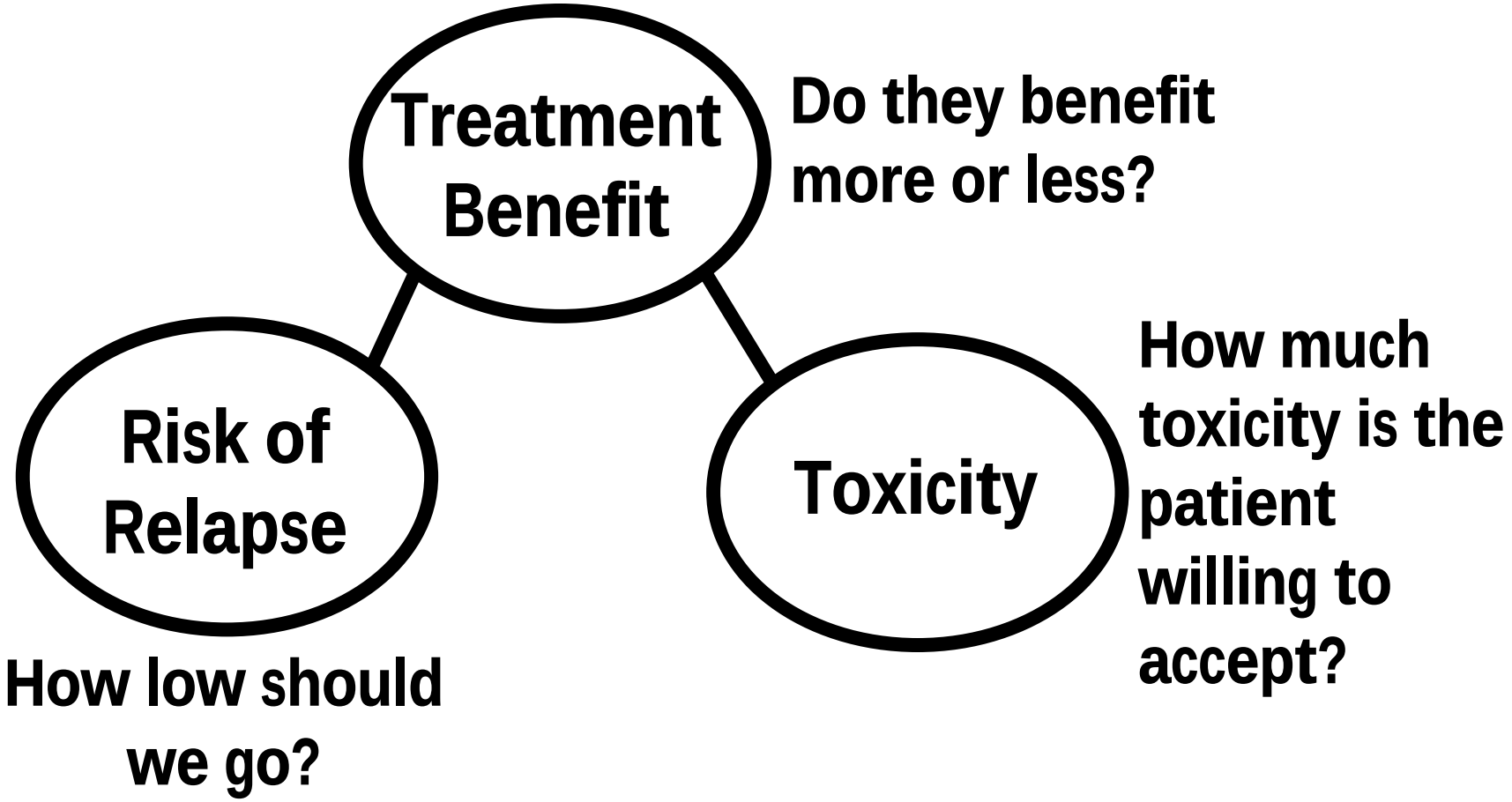
ASSAY	STUDY	TOTAL N	10-yr Risk	95% CI	
BCI	TransATAC	665	3.5%	2.0%	6.1%
PAM50 ROR	TransATAC +ABCSG08	2,137	2.4%	1.6%	3.5%
Endo Predict	ABCSG06 +ABCSG08	1,702	3.7%	0.9%	5.5%

Potential absolute % reduction of distant recurrence with extended endocrine therapy:

- **0.8-3.1% at 10-years**
- **2.9-5.6% at 15 years** (*assuming 1% annual recurrence hazard rate)

Sgroi Lancet Oncol 2013, Sestak JCO 2015, Dubsky BJC 2013

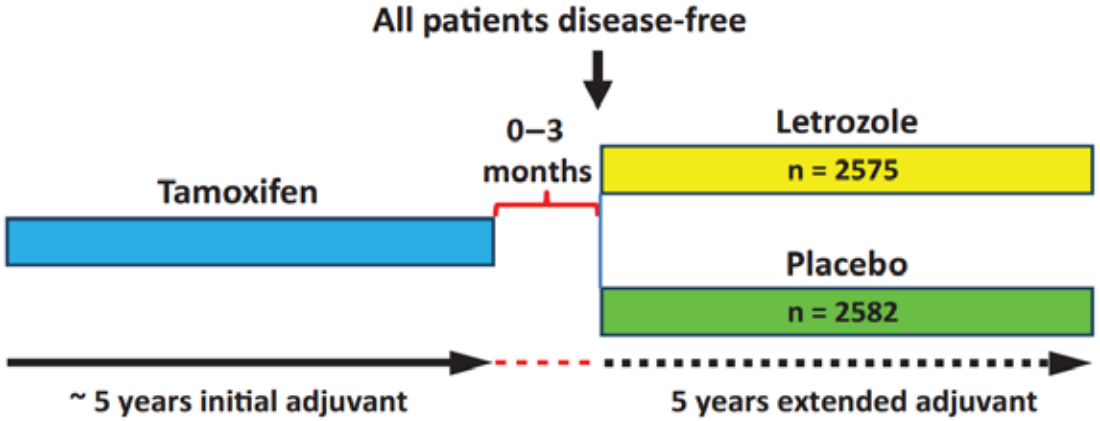
Withdrawing extended endocrine therapy based on current prognostic gene expression-based assays?

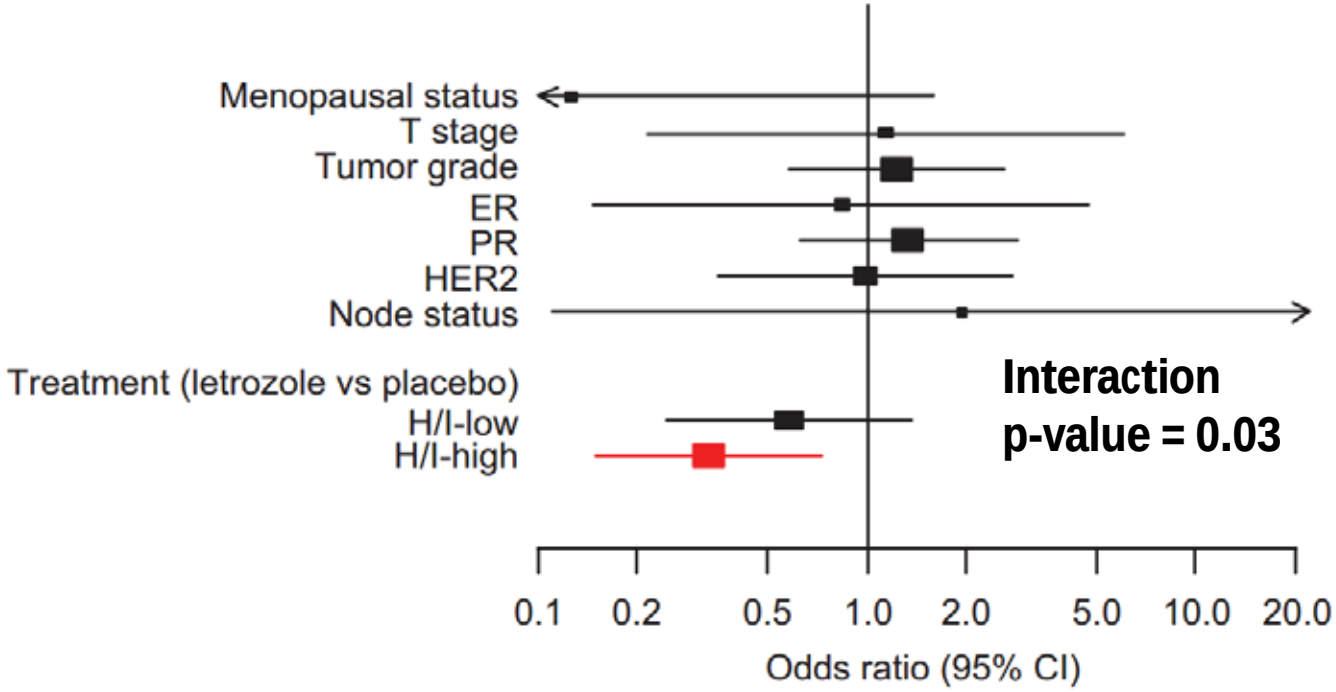


Prediction of Late Disease Recurrence and Extended Adjuvant Letrozole Benefit by the HOXB13/IL17BR Biomarker

Dennis C. Sgroi, Erin Carney, Elizabeth Zarrella, Lauren Steffel, Shemeica N. Binns, Dianne M. Finkelstein, Jackie Szymonifka, Atul K. Bhan, Lois E. Shepherd, Yi Zhang, Catherine A. Schnabel, Mark G. Erlander, James N. Ingle, Peggy Porter, Hyman B. Muss, Katherine I. Pritchard, Dongsheng Tu, David L. Rimm, Paul E. Goss

- Retrospective analysis of samples of the MA.17 clinical trial
- Nested case-control design: 83 recurrences vs 166 non-recurrences à N= 249 patients





JNCI 2013

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

EXTENDED ENDOCRINE THERAPY

HR+/HER2-neg and NODE-negative

	INDICATION	Evidence Quality	Recommendation Strenght
EndoPredict	NO	INTERMEDIATE	MODERATE
PAM50 ROR	NO	INTERMEDIATE	MODERATE

HR+/HER2-neg and NODE-positive

No comment

J Clin Oncol 2016

Are these assays the same at the individual patient level?

NO

Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial

N=313 ONCOTYPEDX, MAMMAPRINT and PROSIGNA

Table 4. Kappa statistics for tests providing risk predictions*

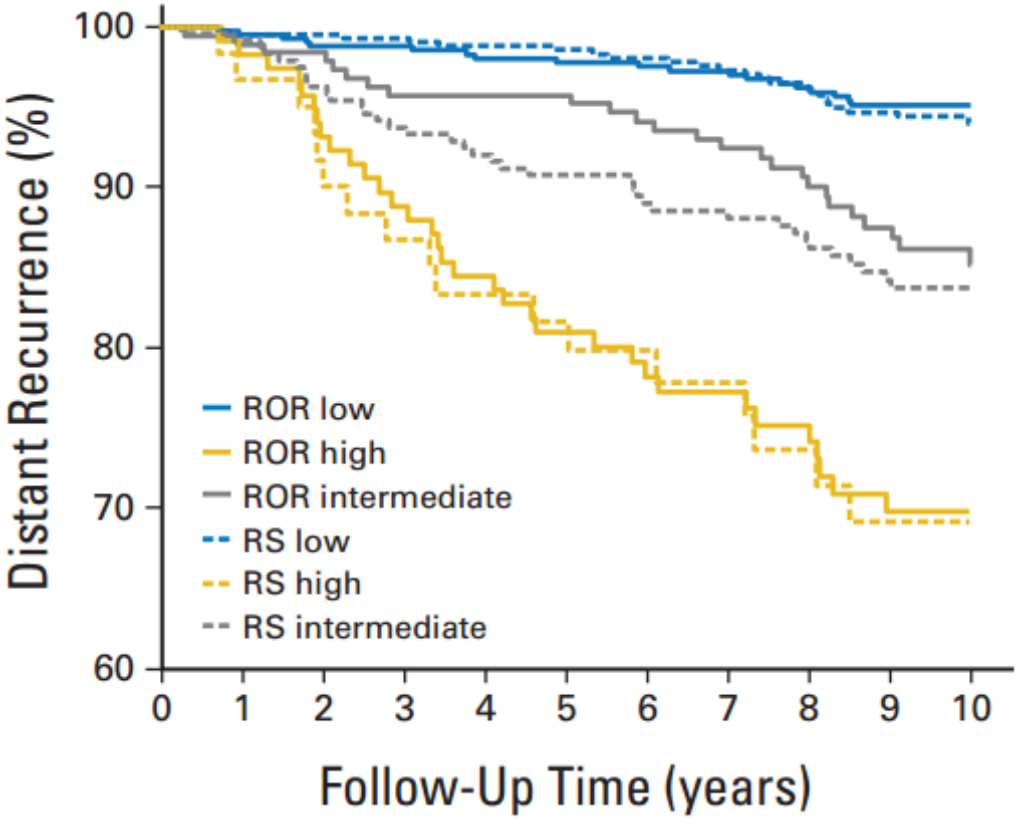
Test	MammaPrint (low), Kappa statistic (95% CI)	Prosigna (low/intermediate), Kappa statistic (95% CI)	IHC4 (low/intermediate), Kappa statistic (95% CI)	IHC4-AQUA† (low/low-mid), Kappa statistic (95% CI)
Oncotype DX (recurrence score ≤25)	0.40 (0.30 to 0.49)	0.44 (0.33 to 0.54)	0.53 (0.41 to 0.65)	0.40 (0.30 to 0.51)
MammaPrint	–	0.53 (0.43 to 0.63)	0.33 (0.21 to 0.44)	0.42 (0.30 to 0.53)
Prosigna (low/intermediate)	–	–	0.39 (0.27 to 0.50)	0.43 (0.31 to 0.54)
IHC4 (low/intermediate)	–	–	–	0.60 (0.50 to 0.70)

- **Only 39.4% were classified uniformly.**
- **Regarding subtype, 40.7% patients had discordant calls (BLUEPRINT vs PROSIGNA).**
- **BLUEPRINT was trained on IHC, while PROSIGNA was trained on natural patterns from gene expression data.**
- **For the individual patient, tests may provide differing risk categorization and subtype information.**

Bartlett et al. JNCI 2016

Comparing PAM50/Prosigna ROR vs. OncotypeDX RS

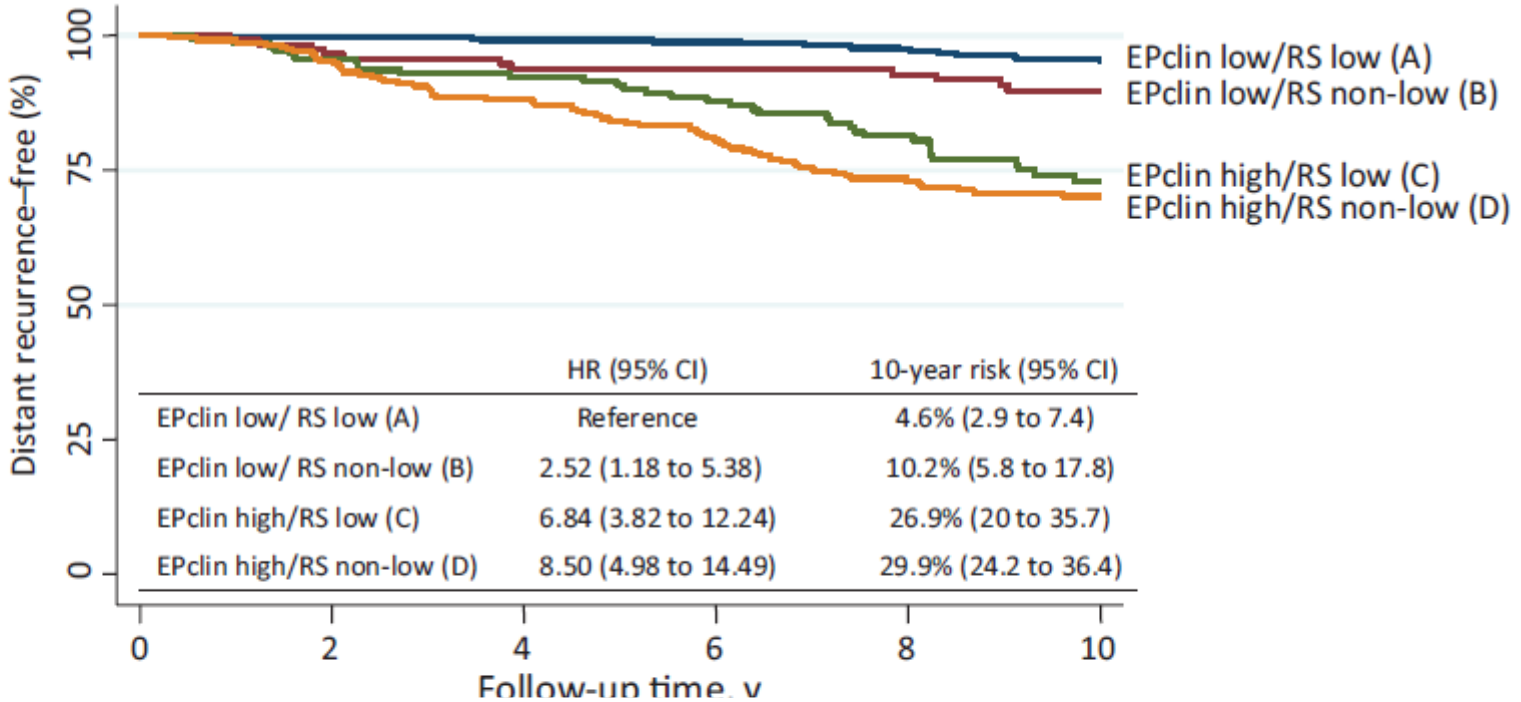
- **N=1,017 patients with ER+ disease treated with 5-years of adjuvant endocrine therapy**
- PROSIGNA ROR provides **more prognostic information**



Dowsett et al. JCO 2013

Comparing EndoPredict (EPclin) vs. OncotypeDX RS

- **N=928 patients with ER+ disease treated with 5-years of adjuvant endocrine therapy**
- **EPclin** provides **more prognostic information**
- **This was partly but not entirely** because of EPclin integrating molecular data with nodal status/tumor size



	HR (95% CI)	10-year risk (95% CI)
EPclin low/ RS low (A)	Reference	4.6% (2.9 to 7.4)
EPclin low/ RS non-low (B)	2.52 (1.18 to 5.38)	10.2% (5.8 to 17.8)
EPclin high/RS low (C)	6.84 (3.82 to 12.24)	26.9% (20 to 35.7)
EPclin high/RS non-low (D)	8.50 (4.98 to 14.49)	29.9% (24.2 to 36.4)

TransATAC

Buus et al. JNCI 2016

Take-home messages

- At least 4 tests based on gene expression are available in Europe.

- All are **standardized/highly reproducible**:
  - MammaPrint and PAM50 à FDA/510(k) cleared.
    - A 10% discordant rate is expected between MammaPrint FF vs. FFPE.
  - EndoPredict and PAM50 can be performed at local labs.

- These tests help **identify patients who do not need adjuvant chemotherapy** because of their low risk of relapsing at 10 years if treated with endocrine therapy-only:

  - IMPORTANT: use them with clinical-pathological variables, mostly tumor size and nodal status.
  - EndoPredict and PAM50 ROR integrate molecular data with tumor size and nodal status.
  - In patients with 2-3 high-risk clinical features treated with endocrine therapy-only, MammaPrint has shown prospectively (MINDACT) that:

    - The low-risk groups has a DMFS >92% at 5-years
    - The DMFS at 10 years of the low-risk is likely to be <90%. More follow-up is needed.
    - A clinically meaningful chemotherapy benefit in this group cannot be excluded.

Take-home messages

- In terms of **predicting the degree of adjuvant chemotherapy benefit**:
  - Evidence exists regarding the predictive ability of OncotypeDX in the high-risk group. However:
    - NSABP-B20 data are confounded by the dataset originally used to generate the assay.
    - SWOG8814 data is hypothesis generating: small sample set and no additional prediction beyond 5 years.
  - Two large phase III prospective clinical trials (**TailorX and RxPonder**) are evaluating the clinical utility of **OncotypeDX** as a predictive test in the following scenarios:
    - TAILORX: Patients with **node-negative**, HR+/HER2-negative disease with Intermediate RS (11-25).
    - RXPONDER: Patients with **1-3 N+**, HR+/HER2-negative disease with Low/Intermediate RS (≤25).
  - One large phase III prospective clinical trial (**OPTIMA**) will evaluate the clinical utility of **Prosigna** as a predictive test in the following scenario:
    - Patients with pN1-2 or pT2(>3cm)pN0 HR+/HER2-negative disease.

Take-home messages

- EndoPredict and Prosigna **predict late recurrence** in HR+/HER2-negative breast cancer.
    - These assays might **identify patients who can be spared extended endocrine therapy** beyond 5 years due to their low risk of relapsing between period 5-10.
    - However, for this indication, the community and the patients might need to establish where to draw the cutoff based on risk, benefit, toxicity and cost (in some countries).
- **Gene expression-based tests should not be considered to be the same**.
    - Head-to-head comparisons for outcome and treatment benefit are needed.
    - To date,
        - Both EndoPredict and Prosigna provided more prognostic information than OncotypeDX in TransATAC.
            - This is only partially explained by the fact that EndoPredict and Prosigna include tumor size and nodal status.

When possible, use these tests!
They are helpful, reproducible and valuable!

THANK YOU!